Genetic, cognitive and social risk mechanisms on depression symptoms in children and adolescents

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Genetic, Cognitive and Social Risk Mechanisms on Depression Symptoms in Children and Adolescents

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Abstract

The last decade has witnessed a proliferation of research dedicated to understanding the aetiology of depression symptoms in children and adolescents. Of particular interest are causes relating to its developmental trajectory, notably the marked rise in symptoms during adolescence. Within this context, the current thesis combined genetic, cognitive and psychosocial approaches to the study of vulnerability in depressive conditions in childhood and adolescence, and extrapolated on any developmental differences in aetiology between these age groups.

Quantitative genetic analysis of data from two large child and adolescent twin samples was utilised to test a progression of research hypotheses. The first study ascertained the nature of genetic and environmental influences in relation to age and sex differences, developmental change, and in extreme-scoring individuals. The second study explored processes of gene-environment correlation and interaction in adolescence. The third study addressed issues relating to the nature of attributional style as a vulnerability factor of depression symptoms. The final study combined psychosocial, cognitive and genetic pathways to the study of depressive outcomes in each sample.

Results suggested developmental differences in the aetiology of depression symptoms. A trend of increasing genetic but decreasing shared environmental effects characterised comparisons of results across age group. 'New' genetic factors emerged in mid-adolescence, whereas 'new' shared environmental influences were implicated in childhood. In adolescence, genetic factors may be expressed through increased exposure towards social stressors, whilst contributing to the susceptibility for these risks. Attributional style may also mediate genetic risks on depressive symptoms in this age range. In contrast this cognitive factor may reflect environmental risks on child depressive symptoms. Specifically it mediated and moderated aspects of social

adversity on child depressive outcomes. The differences in results between children and adolescents are discussed in terms of a developmentally-sensitive aetiological model, which accommodates several different routes to the manifestation of depressive conditions.

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Statement of Authorship

The studies described in Chapters 4 to 7 of this thesis utilise data from two large collaborative studies based at the Social, Genetic and Developmental Psychiatry Centre: the G1219 Study and the Emotions, Cognitions, Heredity and Outcome (ECHO) Study. In each of these studies, I formulated research hypotheses and conducted statistical analyses on the data. In the G1219 study, I was involved in the early stages of data preparation for Wave 3, including data checking, making scales and data entry of missing data. In the ECHO study I tested participants (approximately 90 families), and was data manager from 2004 to 2005. This role involved extracting data from Superlab through Visual Basic macros (Microsoft Excel) and preparing data for use in SPSS. The work presented in this thesis is original and the result of my own work.

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Abbreviations

A list of the *key* abbreviations used in this thesis is provided here. Each abbreviation is also defined when first occurring in the text.

-2LL	Minus twice log likelihood
β	Beta weight (standardised regression coefficient)
μ_{POP}	Population mean
μ_{PRO}	Proband mean
χ^2	Chi-square
$\Delta\chi^2$	Change in χ^2
Δdf	Change in degrees of freedom
$[p_2, p_1]$	Vector representing proband statuses of co-twin and individual
A	Additive genetic factor
a^2	Additive genetic variance component
AIC	Akaike's Information Criterion
B_1	Regression coefficient (of co-twin score on proband score, used in regression model for extremes analysis)
B_2	Regression coefficient (of co-twin score on genetic relatedness, used in regression model for extremes analysis)
BDI	Beck's Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961)
C	Shared environmental factor
c^2	Shared environmental variance component

c_g^2	Group shared environmental effects
C_M	Mean Co-twin scores (used in regression model for extremes analysis)
C_{Score}	An individual's score
CAPA	Child and Adolescent Psychiatric Assessment (Angold et al., 1995b)
CASQ	Children's Attributional Style Questionnaire (Kaslow & Nolen-Hoeksema, 1991)
CBCL	Child Behavior Checklist (Achenbach & Edelbrock, 1983)
CDI	Children's Depression Inventory (Kovacs, 1985)
D	Dominant genetic effects
DD	Dysthymic Disorder
df	Degrees of freedom
DICA	Diagnostic Interview for Children and Adolescents (Welner, Reich, Herjanic, Jung, & Amado, 1987)
DISC	Diagnostic Interview Schedule for Children (Costello, Edelbrock, Kalas, Kessler, & Klaric, 1982)
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (fourth edition)
DZ	Dizygotic (twins)
DZF	Dizygotic female (twins)
DZM	Dizygotic male (twins)
DZO	Dizygotic opposite-sex (twins)

E	Non-shared environmental factor
e^2	Non-shared environmental variance component
$E_{AS\ /\ DEP}$	Measurement error (phenotypic reciprocal causation model)
e_g^2	Group non-shared environmental effects
ECHO	Emotions, Cognitions, Heredity and Outcome (study)
EPQ-N	Eysenck Personality Questionnaire Neuroticism Scale (Eysenck, Eysenck, & Barrett, 1985)
FS	Full siblings
FSF	Full sibling females
FSM	Full sibling males
FSO	Full sibling opposite-sex
GENESiS	Genetic-Environment Study of Emotional States in Siblings
GxE	Gene-environment interaction
h_g^2	Group heritability
ICD	International Classification of Disorders
ICD-10	International Classification of Disorders (version 10)
K-SADS	Kiddie-Schedule for Affective Disorders and Schizophrenia (Puig-Antich, Blau, Marx, Greenhill, & Chambers, 1978)
LES-A	Life Event Scale for Adolescents (Coddington, 1984)
LES-C	Life Event Scale for Children (Coddington, 1984)
LTE	List of Threatening Experiences Questionnaire (Brugha, Bebbington, Tennant, & Hurry, 1985)

M	Moderator variable
M_{MZ}	Expected MZ Mean
$M_{DZ/FS}$	Expected DZ / FS Mean
MDD	Major Depressive Disorder
MFQ	Mood and Feelings Questionnaire (Angold et al, 1995)
ML	Maximum Likelihood
MZ	Monozygotic (twins)
MZF	Monozygotic female (twins)
MZM	Monozygotic male (twins)
N (or n)	Number (of participants)
n.s.	Non-significant (result)
P	Probability
$p_{C1/\ C2/C3/C4}$	Phenotypic concurrent contributions between variables
$p_{L1/\ L2/L3/L4}$	Phenotypic longitudinal contributions between variables
P_M	Mean Proband scores (used in regression model for extremes analysis)
r	Correlation
R	Coefficient of genetic relatedness between co-twin and proband (used in regression model for extremes analysis)
$r_{A(MZ/DZ/FS)}$	Genetic relatedness between twin or sibling pairs
$r_{A(AS\text{-}DEP)}$	Genetic correlation between attributional style and depression symptoms
$r_{C(MZ/DZ/FS)}$	Shared environmental relatedness between twin or sibling pairs

$r_{C(AS\text{-}DEP)}$	Shared environmental correlation between attributional style and depression symptoms
r_{DZ}	DZ twin correlation
$r_{E(AS\text{-}DEP)}$	Non-shared environmental correlation between attributional style and depression symptoms
r_{FS}	Full sibling correlation
rG-E	Gene-environment correlation
r_{MZ}	MZ twin correlation
RMSEA	Root Mean Squared Error Approximation
SD	Standard Deviation
SDQ	Strengths and Difficulties Questionnaire (Goodman, 1997)
SES	Socio-Economic Status
SMFQ	Short Mood and Feelings Questionnaire (Angold et al, 1995)
SPQ	Social Problems Questionnaire (Corney, 1988)
t^2	Twin similarity variance component
T1 (T2, T3)	Time-point 1 (Time-point 2, Time-point 3)
TEDS	Twins Early Development Study
V_p	Variance of a phenotype
$V_{P(twin)}$	Variance of a twin's phenotypic score
$V_{P(sibling)}$	Variance of a sibling's phenotypic score

List of Publications Relevant to this Thesis

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Aims and Overview of the Thesis Structure

There are eight chapters in this thesis. Chapter 1, *Depression in Children and Adolescents*, reviews studies examining the phenomenology and epidemiology of child and adolescent depression and highlights particular findings which require theoretical explanation when considering aetiological models of depression. Chapter 2, *Theories of Depression in Children and Adolescents*, introduces three main theories of depression, which form the basis of this thesis. First, there is a brief introduction to the principles of behavioural genetic studies, followed by a summary of the field's contributions towards understanding child and adolescent depression. Second, the chapter reviews the basic tenets of an influential cognitive theory called the reformulated learned helplessness model of depression, highlighting recent findings and issues in the area. The third section traces the theoretical progression which has characterised psychosocial explanations of depression. Finally, based on conclusions drawn from these literature reviews, the chapter ends with an outline of the current study hypotheses. Chapter 3, *Methodology and Samples*, describes the methods used in this thesis, including the basic assumptions and techniques and the two samples used.

Chapters 4 to 7 present results from testing the different study hypotheses outlined in Chapter 2. Each Chapter begins with a brief introduction and background of the hypotheses tested, followed by a more detailed description of the specific model-fitting analyses used. Results are presented next with a final summary and discussion of specific limitations. Chapter 4, *Genetic and Environmental Influences on Child and Adolescent Depression Symptoms*, examines the nature of genetic and environmental effects on depressive symptoms with respect to age, sex, developmental change and in extreme-scoring individuals. Chapter 5, *Gene-Environment Interplay on Adolescent Depression symptoms*, investigates correlations and interactions between genetic factors

and two social risk measures, negative life events and maternal punitive discipline, on depression symptoms. Chapter 6, *Attributional style as a Cognitive Risk Factor of Child and Adolescent Depression Symptoms*, addresses several issues relating to the role of attributional style as a vulnerability factor for depressive symptoms across development. Finally Chapter 7, *Psychosocial Risk Mechanisms of Child and Adolescent Depression Symptoms*, assesses mediating and moderating routes through which social risks are exerted on depression symptoms, in the context of genetic and cognitive explanations. Thus the combined effects of these different risk mechanisms are investigated. Chapter 8, *Discussion and Conclusions*, summarises the main findings from Chapters 4-7 and considers general limitations across studies. Tentative interpretations and implications of these results are also drawn, before presenting directions for future research and clinical practice.

Chapter 1: Depression in Children and Adolescents

1.1. Introduction and Overview

"Dementors are among the foulest creatures that walk this earth. They infest the darkest, filthiest places, they glory in decay and despair, they drain peace, hope and happiness out of the air around them. Even Muggles feel their presence, though they can't see them. Get too near a Dementor and every good feeling, every happy memory, will be sucked out of you. If it can, the Dementor will feed on you long enough to reduce you to something like itself – soulless and evil. You'll be left with nothing but the worst experiences of your life."

"Harry Potter and the Prisoner of Azkaban" (Rowling, 2000).

In this passage, taken from the third book of her highly successful children's series, J.K. Rowling (2000) describes the recent encountering of a Dementor by the adolescent 15 year old Harry Potter. Beyond the surface descriptions of these creatures, the feelings evoked by their presence are remarkably similar to several of the key symptoms of depression, including dysphoric mood, hopelessness, anhedonia and negative thinking. Whether this analogy was intended by the author, it is interesting that within a highly popular children's book, fictional metaphors of depression symptoms may be comprehensible and perhaps even familiar to a young audience. However this recognition that children and adolescents are able to experience symptoms resembling those of adult depressive conditions is a relatively recent development (Pearce, 1978). Previously, it was thought that due to limited cognitive, emotional and physiological capacities, preadolescent children did not suffer from depression, whereas for adolescents, depression was regarded as a normal developmental feature of the 'adolescent-turmoil' period, which did not require special attention (Harrington, 2002).

These views changed in the 1980s when it became evident that adult cases of depression often had their roots in childhood and adolescence (Costello, et al, 2002), and diagnostic criteria for depressive disorders were extended to include child- and adolescent-onset cases (American Psychiatric Association, 1980). Since then there has been a substantial increase in studies examining the nature of depression in these younger age groups. The aim of this chapter is to present a broad overview of findings relating to how depression is defined and assessed in childhood and adolescence, its developmental continuity and its prevalence in the general population. These descriptive findings provide the background upon which models of aetiology are built.

1.2. Definitions of Depression

Although depression typically refers to manifestations of persistent low mood, clinically, it can sometimes occur among episodes of extreme mood fluctuations, from low mood to elevation and mania. The first of these varieties is unipolar depression, whilst the second is referred to as bipolar or manic depression. This thesis has only focussed on depression characterised by persistent low mood, and as such only definitions relevant to unipolar depression in children and adolescents are described.

Unipolar depression is characterised primarily by mood disturbances, commonly in the form of dysphoric mood and a loss of enjoyment or pleasure (anhedonia). These mood-related symptoms are conceptualised as comprising a disorder when they co-occur with other symptoms, follow a specifiable time-course and inflict some level of psychosocial impairment. The most widely used classification systems, which have standardised and operationalised these criteria are the Diagnostic and Statistical Manual of Mental Disorders (DSM: American Psychiatric Association, 1980) and the International Classification of Disorders (ICD: World Health Organisation, 1980). The latest revision of the DSM, the fourth edition, requires that for a diagnosis of Major Depressive

Disorder (MDD), either depressed mood or anhedonia must be present for a two-week period, in addition to 4 other symptoms occurring in the same time-frame (American Psychiatric Association, 2000). These can include significant weight change, sleep disturbance, psychomotor agitation or retardation, fatigue or low energy, feelings of worthlessness or guilt, decreased concentration and decisiveness, and recurrent thoughts of death and suicide. Dysthymic Disorder (DD) involves similar symptomatology, of which only 3 symptoms must be present most of the time for at least a year (two years in adults). ICD version 10 lists a comparable set of symptoms but also includes reduced self-esteem and confidence, pessimistic views for the future and diminished appetite. Depression is categorised as mild, moderate or severe depending on the number of symptoms reported in a time frame of two weeks (World Health Organisation, 2003).

Whilst a categorical definition of depression encompasses a list of mood-related symptoms, each individual symptom can also be defined as a dimensional construct. In this alternative way of conceptualising depression, normal variation in the extent to which a symptom is endorsed, for example depressed mood, is thought to form a continuum. This dimensional approach is not necessarily incompatible with the categorical approach, and depressed mood and disorder can be viewed as occurring on the same continuum of liability. According to this combined perspective, those with a disorder represent the subset of individuals falling at the extreme end of the spectrum, who for treatment purposes must be categorically defined at a pre-specified threshold.

There is some support for this perspective of a continuum of depressed mood. First, high but subthreshold symptoms of depression carry risk for the development of depressive disorders over time (Rueter, Scaramella, Wallace, & Conger, 1999). Second, both clinical and subthreshold symptoms are associated with psychosocial impairment (Lewinsohn, Rohde, & Seeley, 1998), and moreover, the level of impairment is a linear function of the number of symptoms reported (Pickles et al., 2001). As such, reaching

the diagnostic symptom threshold holds no particular implication for additional impairment. Third, individuals ascertained from the community as depressed 'cases' are phenomenologically similar to those diagnosed clinically (Roberts, Lewinsohn, & Seeley, 1995) with minor exceptions in that thoughts of death and suicide were more readily endorsed by individuals in clinical settings and symptoms of weight/appetite and sleep disturbance were more common in the community sample.

In summary, depression can be defined as both a category and as a dimension. Recent approaches towards resolving these alternate definitions have suggested that depressed mood varies on a continuum of severity with depressive disorder.

1.3. Developmental Differences in Depression

An important issue to consider when defining and assessing depression in young people is whether child- and adolescent-onset depression reflect the same condition. Continuity of depression across development can be considered at two levels (Weiss & Garber, 2003). First, there may be continuity (or change) at the level of symptom presentation, which is the extent to which behavioural manifestations of depression are similar at different developmental periods. Second, there may be continuity within individuals, that is, whether individuals reporting depression symptoms at one time-point are likely to experience symptoms at a later developmental stage. Each level of developmental continuity will be discussed.

1.3.1. Developmental changes in phenomenology

According to DSM-IV and ICD-10 criteria, there are no major differences in the phenomenology of depression across age levels with exception to irritability, which is considered as an age-specific manifestation of depressed mood in children by DSM-IV (American Psychiatric Association, 2000). However this assumption has been queried

by developmental psychopathologists who have argued that manifestations of depression may depend on an individual's level of cognitive, emotional, social and physiological development (e.g. Cicchetti & Schneider-Rosen, 1984).

Consistent with these developmental hypotheses are age effects on motivational and neurovegetative aspects of depression, such as hypersomnia, weight gain, pessimism and social withdrawal, which become increasingly prevalent in adolescents compared to children (Kovacs, Obrosky, & Sherrill, 2003). Similarly, severe cognitive and psychomotor impairments such as memory difficulties, slowed speech, thinking and body movements, and the presence of psychotic features are more likely to characterise older adult depressives compared to their younger counterparts (American Psychiatric Association, 2000). A more systematic comparison of developmental differences between children, adolescents and adults was conducted by a meta-analysis of 11 studies. This revealed significant variability in most of the core symptoms of depression including depressed mood and anhedonia across development (Weiss & Garber, 2003). However it was not clear from the pattern of results whether particular symptoms showed increased or decreased prevalence across age levels, and whether differences emerged between childhood and adolescence, or adolescence and adulthood.

There is also some evidence that the combination of symptoms comprising the phenotype changes with development. For example, differences in the factor structure of depression between children and adolescents have been reported (Achenbach & Edelbrock, 1983; Weiss et al., 1992). In both studies, items pertaining to guilt, low self-esteem and externalising behaviours accounted for most of the variance on a general 'depressed' factor in children, whereas for adolescents, affective items (sadness, loneliness and irritability) and vegetative items (anhedonia and fatigue) were more strongly associated with this latent factor. Whilst these age-related changes in the expression of depression are clearly in need of further investigation, they highlight a

number of issues that should be considered with respect to defining and assessing depression at different developmental stages. More importantly they raise the question of whether different behavioural manifestations associated with child, adolescent and adult depressive symptoms are reflective of the same underlying condition.

1.3.2. Within-individual stability

In contrast to examining developmental continuity of the behavioural presentation of depression, continuity can also be defined at the level of individuals, referring to whether individuals reporting depression symptoms at one time-point are at risk for later depression (Weiss & Garber, 2003). Measuring continuity within individuals requires longitudinal designs, where symptom data from the same individuals are collected at different time-points. Predictive associations across data-points implicate the degree of developmental continuity in the liability associated with depression.

Several studies have reported strong associations between child internalising symptoms and adolescent mood disorders (e.g. Roza, Hofstra, van der Ende, & Verhulst, 2003), adolescent depressive symptoms and adult depressive disorders (e.g. Pine, Cohen, Cohen, & Brook, 1999) and child depressive disorders and recurrent episodes in adulthood (e.g. Harrington, Fudge, Rutter, Pickles, & Hill, 1990). Together these findings demonstrate that definitions of depression in children and adolescents predict those in adulthood, suggesting that there is some stability in the underlying liability characterising conditions experienced at different levels of development.

In summary, these two different definitions of continuity have important implications for developmentally-sensitive models of depression. Findings suggest that although there are normative developmental changes in the *form* of depression across different age groups, there is also evidence of continuity in these age-specific manifestations across time. This suggests that stable within-individual factors influence depression at

each age, thus accounting for longitudinal associations across time. However, there are also developmentally-sensitive factors, which only influence behaviours at a particular age and account for changes in manifestations of depression across time.

1.4. The Assessment of Depression in Children and Adolescents

There are a number of ratings tools that can be used to assess depression in children and adolescents. Choice of instrument usually depends on the definition of depression used (category or dimension) and issues relating to the identity of the informant.

1.4.1. Methods of assessment

Categorical or clinical definitions of depression are typically assessed using diagnostic interviews, and which are based on the operational criteria outlined in DSM-IV or ICD-10. In addition to assessing the presence of a list of symptoms, specific questions on time-course and functional impairment are often included. Most interviews also contain sections covering other disorders, allowing for identification of comorbid conditions. Interviews can differ according to how structured they are and whether they are administered by a clinician or lay person. The outcome measure is typically dichotomous, indicating either the presence or absence of a certain diagnosis. Examples of interviews that are widely used for assessing disorders in children and adolescents are the Diagnostic Interview Schedule for Children (DISC: Costello, Edelbrock, Kalas, Kessler, & Klaric, 1982), the Diagnostic Interview for Children and Adolescents (DICA: Welner, Reich, Herjanic, Jung, & Amado, 1987), the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS: Puig-Antich & Chambers, 1978) and the Child and Adolescent Psychiatric Assessment (CAPA: Angold et al., 1995).

Measures of normal variation in depressive symptomatology are usually assessed through questionnaires although some studies use observational techniques to rate

behaviours in certain settings. There are two types of questionnaires, those which solely measure depression symptoms and those that assess several dimensions of child and adolescent behaviours, including depression-related symptoms. Both types of questionnaire typically consist of a number of items ascertaining the presence and frequency of current symptoms. Depending on the number of behavioural dimensions assessed and the resulting factor structure of the questionnaire, items are often summed to make either sub-scale scores or one composite score, both of which form continuous measures indexing the severity of symptoms. Important considerations when using questionnaire data are reliability including internal consistency of items and test-retest over a period of time, and construct, criterion and concurrent validities. Issues of sensitivity and specificity may also be relevant to the assumptions of a dimensional approach as these statistics index the extent to which high symptom scores represent the same constructs as a clinical diagnosis of depression (e.g. Clark & Harrington, 1999).

Questionnaires that have been developed specifically to assess depression symptoms in child and adolescent samples include the Mood and Feelings Questionnaire (MFQ: Angold et al., 1995a) and the Children's Depression Inventory (CDI: Kovacs, 1985). The Mood and Feelings Questionnaire is generally the preferred scale given that it shows good sensitivity and specificity in relation to diagnostic categories (Thapar & McGuffin, 1998). However the Children's Depression Inventory, which is based on a downward adaptation of Beck's Depression Inventory (BDI: Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) was designed specifically for use among school-aged children as well as adolescent populations, and is thus considered a more 'child-friendly' tool. More general questionnaires such as the Children's Behavioural Checklist (CBCL: Achenbach & Edelbrock, 1983) and the Strengths and Difficulties Questionnaire (SDQ: Goodman, 1997) span a number of common child behavioural problems. In these measures depressive-related items are summed independently to index this phenotype.

1.4.2. Identity of Informant

Information for completing diagnostic interviews and questionnaires can be ascertained from different sources including self-reports, parent-reports and sometimes teacher-reports. From a clinical perspective, data collected from multiple informants is the most useful, however for research studies, this is often time consuming and costly. As such, studies typically select the informant who can provide the most valid information.

Given that symptoms of depression are internalising problems, of which many are covert, it has been argued that self-reports are the most valid and direct means of collating this information (Reynolds, 1994). In contrast, parents and teachers may only detect overt or external signs of depression. Consistent with this, poor inter-rater agreement, particularly between parents and offspring has been found (Cantwell, Lewinsohn, Rohde, & Seeley, 1997; Youngstrom, Loeber & Stouthamer-Loeber, 2000). Studies following up the reasons for this low level of agreement have shown that different informants indeed rate different behaviours (Achenbach, McConaughy, & Howell, 1987). For example, in one study children were three times more likely to report self-dislike, feelings of deja vu, general anxiety, obsessions, suicidal ideation and suicidal attempts, than their parents. Symptoms of hypersomnia, increased appetite, anhedonia and exaggerated illness behaviours were in comparison rated more frequently by parents (Barrett et al, 1991). Thus whereas children tend to rate affective/neurotic signs, parents focus on observable behaviours. Notably however child-rated depressive symptoms were demonstrated to be concordant with clinical diagnoses when compared with other forms of child psychopathology (Rubio-Stipec et al., 1994).

An important consideration when deciding to use child-reports is the chronological age of the sample, and more specifically their associated level of cognitive and emotional development. As this will undoubtedly influence language and reading comprehension

abilities, knowledge of emotion and mood, self-awareness and time concepts, this will have implications for the validity of data gathered, especially from younger children, who may not yet possess these skills (Kovacs, 1986). Studies examining these issues have shown that children aged between 8 and 10 have acquired the reading and language comprehension skills needed for the completion of these assessments, and can differentiate between basic emotions, and self and other perspectives on these (see Harrington, 1993 for a review). The emergence of self-awareness also becomes more apparent as children reach middle childhood (between ages 6 to 9), when they begin to describe themselves in terms of psychological aspects such as competencies rather than concrete features such as favourite activities and physical characteristics. However despite these increasingly sophisticated capacities, children in this age range may still experience difficulties conceiving the temporal order of their symptoms and the duration with which these last (Kovacs, 1986). Thus although children are able to report on *current* depressed mood and symptoms, they may be less proficient in providing information on time course or previous episodes (Harrington, 1993).

In summary, depression can be assessed using diagnostic interviews, which assume categorical definitions of the phenotype, or questionnaires, which are continuous measures. It has been demonstrated that older children and adolescents can report accurately and reliably on their emotions, although parent and teacher reports can offer complementary sources of information. Depending on the aspect of the phenotype investigated, individual studies may vary in the informants used to provide data.

1.5. Prevalence rates of Depression in Children and Adolescents

Over 50 community samples have reported prevalence estimates of unipolar depression in children and adolescents. These are listed in Table 1.1. It is immediately apparent that wide discrepancies exist in depression rates across different studies. These variations

may be due to several methodological differences, most notably how depression has been defined and if information has been gathered from different informants. Although the majority of studies in Table 1.1 have used diagnostic interviews that yield DSM-compatible diagnoses of major depression, the additional criteria of psychosocial impairment has not been consistently applied. Consequently more conservative estimates of the proportion of depressive 'cases' have been identified (e.g. Bird et al., 1987; Canino et al., 1987). An additional source of variation lies with studies utilising dimensional approaches, which involve less stringent criteria compared to categorical ones. These can be divided into those identifying individuals with high but subthreshold symptoms, individuals endorsing a single item of mood disturbance (usually depressed mood) or individuals scoring above a certain cut-off point on a questionnaire. As can be seen in Table 1.1, the prevalence estimates of these 'cases' are generally larger (e.g. Goodyer & Cooper, 1993; Kashani et al, 1987; Shaaban & Baashar, 2003).

A final difference between studies is whether data from different informants has been used and if so, how these have been combined. Where self and parent informed diagnoses are presented separately, children and adolescents tend to report higher rates of depression (Fergusson, Horwood, & Lynskey, 1993; Puura et al., 1998; Shaffer et al., 1996; Verhulst, van der, Ferdinand, & Kasius, 1997). Moreover, there is often little agreement between informants on whether depression is present. Prevalence rates range from 0.4% when there is complete agreement between parent and child to 3.6% when either parent or child report a positive diagnosis (Verhulst et al, 1997). Studies which have aggregated information from parents or individuals are not always clear in how sources are combined, and range from use of computer algorithms to clinical judgement.

Table 1.1: Epidemiological studies examining prevalence estimates for unipolar depression in children and adolescents.

Authors	Age	Time Frame	Prevalence (%) of depression			
			Diagnostic[a]	Subclinical	Symptom	Questionnaire
I. Child samples						
Kashani, Holcomb, & Orvaschel, 1986	2-7	Current	1.0		8.0	
Ford, Goodman, & Meltzer, 2003	5-7	Current	0.1			
Fleming, Offord, & Boyle, 1989	6-11	Current	0.6			
Costello et al., 1988	7-11	1 year	0.4			
Kashani & Simonds, 1979	7-12	Current	1.9		17.4	
Kashani, Orvaschel, Rosenberg, & Reid, 1989	8	Current	1.4		17.1	
Esser, Schmidt, & Woerner, 1990	8	Current	6.0		11.6	
Almqvist et al., 1999	8-9	Current	6.2			24.0
Puura et al, 1998	8-9	Current	3.2 (5.9)[b]			7.1
Ford et al, 2003	8-10	Current	0.3			
Fombonne, 1994	8-11	3 months	0.3			
Polaino-Lorente & Domenech, 1993	8-11	Current	1.8			7.3
Polaino-Lorente, Mediano Cortes, & Martinez, 1997	8-11	Current	4.0			
Kashani et al., 1983	9	Current	1.8			
		1 year	1.1			
Costello, Mustillo, Erkanli, Keeler, & Angold, 2003	9-10	3 months	0.5			
Velez, Johnson, & Cohen, 1989	9-12	Current	2.5			
Anderson, Williams, McGee, & Silva, 1987	11	1 year	1.8		6.4	
McGee, Feehan, Williams, & Anderson, 1992	11	Current	0.5			
Hankin et al., 1998	11	1 year	1.1			
Costello et al., 2003	11	3 months	1.9			

[a] These prevalence rates refer only to major depression or depressive disorder as defined in DSM or ICD. Estimates for dysthymic disorder and minor depression have not been included in this table.

[b] Parent and child-reported diagnoses are presented separately with estimates of child-reported depression in brackets

Table 1.1 Continued

Authors	Age	Time Frame	Prevalence (%) of depression			
			Diagnostic[a]	Subclinical	Symptom	Questionnaire
Ford et al., 2003	11-12	Current	0.7			
Kashani et al., 1989	12	Current	1.4		24.3	
Costello et al., 2003	12	3 months	0.4			
II. Adolescent samples						
Garrison, Schluchter, Schoenbach, & Kaplan, 1989	12-15	Current	4.4			
Schoenbach, Kaplan, Grimson, & Wagner, 1982	12-16	Current	2.9		15.0	
Fleming et al., 1989	12-16	Current	1.8			
Shaaban & Baashar, 2003	12-19	Current	4.2	8.6		11.0
Frost, Moffitt & McGee, 1989	13	Current	1.5			
Esser et al., 1990	13	Current	5.8		29.9	
Hankin et al., 1998	13	1 year	2.1			
		Lifetime	3.2			
Costello et al., 2003	13	3 months	2.6			
Ford et al., 2003	13-15	Current	2.5			
Verhulst et al., 1997	13-18	6 months	1.3 (2.8)[b]			
Velez et al., 1989	13-18	Current	3.7			
Costello et al., 2003	14	3 months	2.7			
Kashani et al., 1987	14-16	Current	4.7	22.0	19.0	
Whitaker et al., 1990	14-17	Lifetime	4.0			
Oldehinkel, Wittchen & Schuster, 1999	14-17	Current	6.7	5.3		
		1 year	3.4	3.5		

[a] These prevalence rates refer only to major depression or depressive disorder as defined in DSM or ICD. Estimates for dysthymic disorder and minor depression have not been included in this table.

[b] Parent and child-reported diagnoses are presented separately with estimates of child-reported depression in brackets

Table 1.1 Continued

Authors	Age	Time Frame	Prevalence (%) of depression			
			Diagnostic[a]	Subclinical	Symptom	Questionnaire
Lewinsohn, Hops, Roberts, Seeley, & Andrews, 1993	14-18	Current	2.6			
		Lifetime	18.5			
	15-19	Current	3.1			
		Lifetime	24.0			
McGee et al., 1990	15	Current	1.2			
		1 year	1.9			
McGee et al., 1992	15	Current	2.5			
Fergusson et al., 1993	15	Current	0.5 (0.7)[b]			
		1 year	2.2 (4.2)[b]			
Hankin et al., 1998	15	1 year	2.8			
		Lifetime	5.7			
Costello et al., 2003	15	3 months	3.7			
Velez et al., 1989	15-20	Current	3.1			
Costello et al., 2003	16	3 months	3.1			
Levy & Deykin, 1989	16-19	Current	6.6			
Deykin, Levy, & Wells, 1987		Lifetime	6.8			
Olsson & von Knorring, 1999	16-17	Current				12.3
		1 year	5.8	2.4		
		Lifetime	11.4			
Kashani et al., 1989	17	Current	5.7		48.6	
Reinherz, Giaconia, Lefkowitz, Pakiz, & Frost, 1993	18	Current	2.9			
		6 months	6.0			
		Lifetime	9.4			

[a] These prevalence rates refer only to major depression or depressive disorder as defined in DSM or ICD. Estimates for dysthymic disorder and minor depression have not been included in this table.

[b] Parent and child-reported diagnoses are presented separately with estimates of child-reported depression in brackets

Table 1.1 Continued

Authors	Age	Time Frame	Prevalence (%) of depression			
			Diagnostic[a]	Subclinical	Symptom	Questionnaire
Feehan, McGee, Raja, & Williams, 1994	18	Current	3.4			
Hankin et al., 1998		1 year	16.8			
		Lifetime	20.7			
III. Combined						
Bird et al., 1987	4-16	6 month	5.9			
Canino et al., 2004	4-17	1 year	3.4			
Eapen, Jakka, & Abou-Saleh, 2003	6-18	Current	3.0			
Simonoff et al., 1997	8-13	Current	1.3			
Angold, Costello, & Worthman, 1998	9-13	Current	3.1			
Costello, Farmer, Angold, Burns, & Erkanli, 1997	9-13	Current	0.3			
Shaffer et al., 1996	9-17	Current	3.0 (3.2) [b]			
Pine et al., 1999	9-18	Current	3.0		10.0	
Cohen et al., 1993	10-13	Current	2.0			
Angold et al., 1998	10-14	Current	3.2			
Toros et al, 2004	10-20	Current				12.6
Velez et al., 1989	11-14	Current	2.5			
Angold et al., 1998	11-15	Current	2.7			
Saluja et al, 2004	11-15	Current				18.0
Cooper & Goodyer, 1993	11-16	Current	3.6	8.9		12.2
		1 year	6.0	20.7		
Pine et al., 1999	11-20	Current	3.0		19.0	

[a] These prevalence rates refer only to major depression or depressive disorder as defined in DSM or ICD. Estimates for dysthymic disorder and minor depression have not been included in this table.

[b] Parent and child-reported diagnoses are presented separately with estimates of child-reported depression in brackets

Despite methodological inconsistencies, several noteworthy trends can be observed from Table 1.1. In general, children under the age of 7 are rarely diagnosed with depressive disorders (< 1%) (Ford et al, 2003; Kashani et al, 1986). There is a gradual change in middle childhood between the ages of 7 and 12, where prevalence estimates for diagnostically defined depression ranges from 0.3% (Fombonne et al, 1994; Ford et al, 2003) up to 6.2% (Almqvist et al, 1999). Even larger increases are witnessed in adolescence, reaching as high as 16.8% (Hankin et al, 1998). By late adolescence, lifetime prevalence rates are estimated at a maximum of 24% (Lewinsohn et al, 1993). Similar age trends characterise studies using a dimensional approach. Whereas up to 24% of children between the ages of 7 and 12 report depressed mood as a symptom by adolescence, this estimate is roughly doubled, at 48.6% (Kashani et al, 1989).

This increase in the prevalence of depression from childhood to adolescence is well-documented among the longitudinal studies in Table 1.1 (Bird et al, 1987; Cohen et al, 1993; Cooper & Goodyer, 1993; Costello et al, 2003; Fleming et al, 1989; Ford et al, 2003; Hankin et al, 1998; Kashani et al, 1989; Lewinsohn et al, 1993; Oldehinkel et al, 1999; Simonoff et al, 1997; Shaaban & Baashar, 2003). More interesting is that the rise of depression in adolescence is more marked among girls (Cohen et al, 1993; Costello et al, 2003; Fleming et al, 1989; Hankin et al, 1998; Oldehinkel et al, 1999). In contrast depression has been found to be comparable between girls and boys or in some studies more common among boys, in childhood (Almqvist et al, 1999; Anderson et al, 1987; Esser et al, 1990; McGee et al, 1992; Puura et al, 1998).

The timing of *when* the sex difference emerges in adolescence has received considerable interest. Most studies suggest that it occurs between the ages of 13 and 15 (Cohen et al, 1993; Hankin et al, 1998; McGee et al, 1992; Oldehinkel et al, 1999) but more recent findings on the effects of pubertal status depression rates indicate that chronological age may mask crucial developmental transitions, which might explain this emerging

difference between girls and boys. Consistent with this hypothesis, pubertal status measured by Tanner stages was a better predictor of this expected sex ratio, than age (Angold et al, 1998). Furthermore, the transition to Tanner Stage III during mid-puberty was characterised by an increased female preponderance and a significant reduction in the rates of depression among males. Together these findings implicate an intriguing possibility that changes occurring in mid-puberty account for the age by sex interaction documented by epidemiological studies.

This section has demonstrated that depressive disorders and symptoms are not as uncommon as once thought. The sudden rise in prevalence rates coinciding with mid-puberty suggests that adolescence may be a critical period for increased vulnerability to depressive mood and disorders, especially among girls.

1.6. Concluding remarks

The epidemiological studies discussed in this Chapter are instrumental in sketching out initial themes that subsequently take shape in this thesis. It has been established that depression is of a diagnosable form in childhood and adolescence, and moreover, that its symptoms are experienced not only by a sub-set of clinically referred individuals but also to varying degrees by individuals falling in the normal range. This fact alone ensures that the examination of its aetiology, which is the focus of this thesis is worthy of scientific interrogation. Additionally the wide range of available rating tools for the ascertainment of depression symptoms makes such a study an empirical possibility.

Increased prevalence rates of depression disorders and symptoms in adolescence marks this developmental period as one of particular interest to the search for risk factors. Thus this thesis focuses mainly on adolescent depression. Nevertheless as depression shows continuity across time, that is, children presenting with symptoms are likely to relapse in adolescence and adulthood, studying these processes in childhood offers an

additional lens to view the developmental trajectory of depression. Such developmental mechanisms must address simultaneously the question of what underlies the stability of depression across time within certain individuals in the context of what factors are responsible for age-specific manifestations of depression across these individuals.

In summary, ongoing themes of this thesis are exploring aetiological and vulnerability influences of depression; and considering how and when these emerge across development. The specific aetiological and vulnerability influences which will be examined are discussed in the next Chapter, where several theories of the causes of depression are presented, with speculations as to how these may link with one another. To provide a full explanation of depression, however they must be able to account for the developmental trends outlined in the epidemiological studies of this Chapter.

Chapter 2: Theories of Depression in Children and Adolescents

2.1. Overview

Several interesting features in the presentation, course and epidemiology of depression in children and adolescents were described in Chapter 1. Providing an explanatory framework in which to contextualise these findings, and thus unravel the aetiology and developmental trajectory of depression forms the main research aim of this thesis. Depression has been explored from a spectrum of theoretical perspectives, of which three are considered in detail in this thesis. These are behavioural genetic, cognitive and psychosocial approaches. Behavioural genetic approaches are based on strong theoretical conceptions that genes in combination with environmental risk factors exert causal influences on behavioural outcomes such as depression. Cognitive theories examine intermediate processes defined at the level of thought or information processing, which may confer vulnerability towards depression. Psychosocial theories focus on identifying specific aspects of the environment, which contribute towards certain phenotypes and the mechanisms by which these are expressed. An overview of the principles of each theory and a summary of its findings is provided in this Chapter. Common to all three approaches is the implicit assumption that the presentation of depression is the output of a complex developmental process, unfolding over time. Where they differ is the level of analysis that this process is studied. As such when considered in isolation each theory is relatively restricted in how well it can explain the aetiology of depression. Thus initial links between theories and how these may emerge across development are also discussed. These speculations form the hypotheses examined in subsequent Chapters.

2.2. Behavioural Genetic Approaches

2.2.1. Key Concepts

The fundamental principle governing behavioural genetic approaches is that genetic variation contributes to individual differences in behavioural outcomes (Plomin, DeFries, McClearn, & McGuffin, 2001). According to this, the direction of causation between genes and behaviour is one-way, with naturally occurring variation in the sequencing of DNA molecules, which characterises an individual's genetic make-up, affecting behaviour. Behaviours cannot in turn alter genetic variation except in unusual circumstances, such as exposure to high levels of ionizing radiation, which may lead to genetic mutation. Indexing and quantifying these unambiguous causal relationships between genetic variation and behavioural phenotypes, such as depression comprises a large component of behavioural genetic research.

To this end, quantitative designs have been used to infer and estimate genetic effects by statistical comparisons of the degree of resemblance between different family members, such as identical and non-identical twins or full, half and step siblings (Plomin et al, 2001). These designs assume that the degree of resemblance between two related individuals at a behavioural level varies as a function of their genetic relatedness. However insofar that genes do not account for all the similarity between family members, any remaining variance may also be attributed to the level at which they share their rearing environment. These aspects of the environment that influence phenotypic resemblance among family members are known as shared environmental influences. Given that related individuals also differ in their expression of a phenotype, these are assumed to be due to non-shared (individual-specific) environmental factors. Thus quantitative genetic designs are as important for ascertaining environmental effects on behavioural outcomes, as they are for obtaining evidence for the role of genetic factors.

There are three different types of quantitative genetic study that have been used to explore genetic and environmental effects on depression: family, twin and adoption studies. Whilst earlier studies focussed primarily on quantifying genetic and environmental effects, more recent developments in statistical modelling techniques utilised by these designs have allowed researchers to move beyond estimating simple heritability to exploring a variety of questions relating to the *nature* of genetic and environmental influences. These include age and sex specific effects, continuity across time, rater effects and links between dimensions and disorders; findings which are especially interesting when interpreted against the backdrop of phenomenological and epidemiological findings described in Chapter 1. Also of recent interest and made tangible by the adaptability of analytical techniques, is the question of *how* genetic factors are expressed, in particular the intermediate pathways by which genetic influences interact and correlate with the environment. The remainder of this section is divided into two parts. The first discusses the evidence for genetic effects from a variety of quantitative genetic designs and the nature of these effects. The second presents preliminary findings on how genetic risks may be expressed in psychosocial pathways.

2.2.2. Genetic influences on depression

2.2.2.1. Family studies

By far the simplest method available to determine if variation in a measured phenotype is due to genetic (and/or environmental) effects is to investigate the degree of clustering of such conditions among family members who are genetically related. A higher than chance incidence of depression among first degree relatives is taken as tentative support for mechanisms of heredity. 'Bottom-up' studies have found significantly elevated rates of major depression in first-degree relatives of child probands (Birmaher, Ryan, Williamson, Brent & Kaufman, 1996), whilst top-down studies, have shown that the

offspring of depressed parents are approximately three times more likely to report a lifetime episode of depression than offspring of controls (Weissman, Warner, Wichramaratne, Moreau & Olfson, 1997). Thus both sets of findings converge on the conclusion that depressive conditions runs in families.

A more subtle difference between studies, which has implications for the specificity of the familial transmission of depression, is the *type* of control group used for comparing rates of depression. Levels of depressive disorders in the first degree relatives of probands are either compared to families of normal control individuals free of psychopathology or to the families of psychiatric controls, where individuals may report other psychiatric conditions. A recent meta-analysis of 17 family studies (Rice, Harold, & Thaper, 2002) revealed odds ratios of 2.30 and 3.98 for bottom-up and top-down studies respectively when compared to the family members of normal controls. However when studies used psychiatric individuals as controls, the odds ratios were reduced, at 1.85 and 1.70 for bottom-up and top-down studies respectively. The difference in odd ratios between these study designs suggests that it is not the presence of psychopathology per se which accounts for higher rates of depressive disorder in family members, but that the higher incidence of symptoms in family members is specifically associated with a familial transmission of depression.

In summary there is reasonably consistent evidence that depressive conditions aggregate in families. However as family members are likely to share the same environment as well as genetics, any conclusions drawn from these designs are rather limited in terms of providing a genetic explanation for depression.

2.2.2.2. Twin studies

Twin studies offer a means of partitioning genetic and environmental effects, and findings from these designs form the staple source of support for genetic effects on

depression. In brief, twin analyses exploit naturally occurring differences in the genetic relationship between two types of twin. Monozygotic (MZ) twins originate from the same fertilised ova, and are thus genetically identical. Dizygotic (DZ) twins are created by the simultaneous fertilisation of different ovum and therefore like full siblings, share on average only half of their segregating genes. In addition to genetics, both types of twins also share their rearing or shared environment. Genetic and shared environmental effects are thought to contribute towards the phenotypic similarity observed among twins. Increased resemblance among MZ twin pairs may be due partly to greater genetic similarity and this effect can be estimated from the difference between MZ and DZ twin correlations on a behavioural measure. Twin similarity not accounted for by genetic effects is assigned as shared environmental effects, and can also be estimated from twin correlations. Finally any differences between MZ twins are attributed to non-shared environmental effects. All three sources of influence can be estimated by re-expressing MZ and DZ correlations as structural equations reflecting the shared genetic and environmental components. Applying model-fitting techniques can then yield parameter values which best fit the data. These statistical implementations are described further in Chapter 3 in addition to the assumptions and limitations of twin studies.

The last decade has witnessed an increased effort to recruit large, epidemiological samples of child and adolescent twins. As a result, rather than relying on extrapolation from the adult literature, these findings have offered a blank slate upon which conclusions concerning the heritability of child and adolescent conditions can be drawn. To date, there have been at least 30 published papers assessing genetic (a^2), shared (c^2) and non-shared (e^2) environmental effects on depressive-related phenotypes in children and adolescents. These are summarised in Table 2.1. As some of the analyses described by individual studies were conducted in the same large twin cohort, albeit at different time-points in the study, results quoted may not be entirely independent across studies.

Table 2.1: Quantitative genetic studies examining genetic (a^2) and environmental effects (c^2 and e^2) on child and adolescent depressive phenotypes

Authors (year)	Phenotypic measure(s)	Sample	Rater	Estimates		
				a^2	c^2	e^2
Wierzbicki, 1987	Wessman-Ricks (W-R) Mood Scales	Males & females aged 6-16	Self	0.94		
	Depression Adjective Checklist		Self	0.72		
	Global levels of depression		Parent	0.80		
	Zung's Self-Rating Depression Scale		Parent	0.35		
Hewitt, Silberg, Neale, Eaves, & Erickson, 1992	Child Behaviour Checklist	Males[b] aged 8-11	Combined mother & father	0.70	0.20	0.10
		Females[b] aged 8-11		0.15	0.72	0.13
		Males[a] aged 12-16		0.49	0.41	0.10
		Females[a] aged 12-16		0.53	0.40	0.07
Rende, Plomin, Reiss, & Hetherington, 1993	Children's Depression Inventory	Males & females aged 9-18	Self	0.34	0.02	0.62
		High scoring individuals		0.23	0.44	
Thapar & McGuffin, 1994	Mood and Feelings Questionnaire	Males & females[a] aged 8-11	Parent	0.18	0.60	0.22
		Males & females[a] aged 12-16	Self	0.70	0.00	0.30
			Parent	0.78	0.04	0.18
Edelbrock, Rende, Plomin, & Thompson, 1995	Child Behaviour Checklist	Males & females aged 7-15	Parent	0.50	0.25	0.25
Schmitz, Fulker, & Mrazek, 1995	Child Behaviour Checklist	Males & females aged 2-3	Parent	0.17	0.45	0.38
		Males & females aged 4-8		0.37	0.26	0.37
Gjone, Stevenson, Sundet, & Eilertsen, 1996	Child Behaviour Checklist	High scoring males & females[a] aged 5-6	Parent	0.73	0.01	
		High scoring males & females[a] aged 5-6		0.74	0.00	
		High scoring males & females[a] aged 12-13		0.28	0.48	
		High scoring males & females[a] aged 14-15		0.32	0.39	
Murray & Sines, 1996	Missouri Children's Behaviour Checklist	Males & Females aged 4-6	Parent	0.00	0.29	0.71
		Males & Females aged 4-6		0.46	0.00	0.54

[a] No evidence for sex effects; [b] Significant sex effects

Table 2.1 Continued

Authors (year)	Phenotypic measure(s)	Sample	Rater	Estimates		
				a^2	c^2	e^2
Zahn-Waxler, Schmitz, Fulker, Robinson, & Emde, 1996	Child Behaviour Checklist	Males & females aged 5	Mother	0.56	0.06	0.38
			Father	0.10	0.57	0.34
Eley, 1997	Children's Depression Inventory	Males & females aged 8-16	Self	0.48	0.10	0.42
		High scoring individuals		0.23	0.29	
Deater-Deckard, Reiss, Hetherington, & Plomin, 1997	Child Behaviour Checklist	Wave 1: Males & females aged 9-18	Mother	0.62	0.04	0.34
			Father	0.52	0.25	0.23
		Wave 1: High scoring individuals	Mother	0.38	0.09	
			Father	0.40	0.28	
		Wave 2: Males & females aged 12-21	Mother	0.52	0.08	0.40
			Father	0.59	0.07	0.34
		Wave 2: High scoring individuals	Mother	0.24	0.34	
			Father	0.39	0.26	
Eaves et al, 1997	Child and Adolescent Psychiatric Assessment symptom count	Males aged 8-16	Self	0.11	0.00	0.89
			Mother	0.64	0.00	0.36
			Father	0.72	0.00	0.28
		Females aged 8-16	Self	0.19	0.00	0.81
			Mother	0.66	0.00	0.34
			Father	0.54	0.00	0.46
	Mood and Feelings Questionnaire	Males aged 8-16	Self	0.16	0.14	0.70
			Mother	0.65	0.00	0.35
			Father	0.60	0.00	0.40
		Females aged 8-16	Self	0.15	0.26	0.59
			Mother	0.64	0.00	0.36
			Father	0.60	0.00	0.40

[a] No evidence for sex effects; [b] Significant sex effects

Table 2.1 Continued

Authors (year)	Phenotypic measure(s)	Sample	Rater	Estimates		
				a^2	c^2	e^2
Gjone & Stevenson, 1997	Child Behaviour Checklist	Males & females[a] aged 5-15	Parent	0.34	0.41	0.25
O'Connor, McGuire, Reiss, Hetherington, & Plomin, 1998	Composite depression score: Children's Depression Inventory Behaviour Problem Index Behaviour Events Inventory Observational ratings	Wave 1: Males & females[a] aged 10-18	Combined	0.48	0.07	0.45
		Wave 2: Males & females[a] aged 13-21		0.22	0.14	0.64
Eley & Stevenson, 1999	Children's Depression Inventory	Males[b] aged 8-11	Self	0.08	0.36	0.56
		Females[b] aged 8-11		0.23	0.37	0.40
		Males[b] aged 12-16		0.57	0.01	0.42
		Females[b] aged 12-16		0.02	0.56	0.42
Jacobson & Rowe, 1999	Centre for Epidemiological Studies Depression Scale	Males[b] aged 11-20	Self	0.02	0.29	0.69
		Females[b] aged 11-20		0.44	0.05	0.51
Silberg et al., 1999	Child and Adolescent Psychiatric Assessment symptom count	Males: Prepubertal	Self	0.00	0.00	1.00
		Females: Prepubertal		0.00	0.00	1.00
		Males: Pubertal		0.00	0.00	1.00
		Females: Pubertal		0.28	0.00	0.72
Boomsma et al., 2000	Beck Depression Inventory	Wave 1 males[b] aged 13-22 (mean: 17.7)	Self	0.43	0.00	0.57
		Wave 1 females[b] aged 13-22 (mean: 17.7)		0.49	0.00	0.51
		Wave 2 males[b] aged 15-24 (mean: 17.8)		0.39	0.00	0.61
		Wave 2 females[b] aged 15-24 (mean: 17.8)		0.51	0.00	0.49
Hudziak, Rudiger, Neale, Heath, & Todd, 2000	Child Behaviour Checklist	Males 8-12	Parent	0.65		0.35
		Females 8-12		0.61		0.39
Silberg, Rutter, & Eaves, 2001	Child and Adolescent Psychiatric Assessment symptom count	Females 8-13	Self	0.00	0.25	0.75
		Females 14-17		0.26	0.00	0.74

[a] No evidence for sex effects; [b] Significant sex effects

Table 2.1 Continued

Authors (year)	Phenotypic measure(s)	Sample	Rater	Estimates		
				a^2	c^2	e^2
Happonen et al., 2002	Composite depression score: Children's Depression Inventory Multidimensional Inventory of Children's Behaviour	Males & females[a] aged 11-12	Self	0.45	0.00	0.55
			Parent	0.43	0.19	0.38
		Males[b] aged 11-12	Teacher	0.28	0.39	0.34
		Females[b] aged 11-12		0.42	0.39	0.20
		Males & females[a] aged 11-12	Peer	0.71	0.00	0.29
Rice, Harold, & Thapar, 2002	Mood and Feelings Questionnaire	Males & females aged 8-11	Parent	0.00	0.76	0.24
		High scoring males & females aged 8-11		0.20	0.47	
		Males[b] aged 12-17	Self	0.43	0.10	0.47
		Females[b] aged 12-17		0.31	0.30	0.39
		High scoring males & females[a] aged 12-17		0.14	0.41	
		Males & females aged 12-17	Parent	0.29	0.47	0.24
		High scoring males & females aged 12-17		0.32	0.40	
Bartels et al., 2003; Bartels et al., 2004	Child Behaviour Checklist	Males & females[a] aged 10	Mother	0.36	0.32	0.32
			Father	0.38	0.35	0.27
		Males & females aged 12	Parent	0.37	0.36	0.27
Glowinsky et al (2003)	DSM-IV Major Depressive Disorder	Females aged 12-23	Self	0.40	0.00	0.60
Scourfield et al., 2003	Mood and Feelings Questionnaire	Males[b] aged 5-11	Parent	0.13	0.38	0.49
		Females[b] aged 5-11		0.52	0.24	0.24
		Males & females[a] aged 12-17	Self	0.66	0.00	0.34
		Males[b] aged 12-17	Parent	0.58	0.09	0.33
		Females[b] aged 12-17		0.77	0.03	0.20

[a] No evidence for sex effects; [b] Significant sex effects

Table 2.1 Continued

Authors (year)	Phenotypic measure(s)	Sample	Rater	Estimates		
				a^2	c^2	e^2
van der Valk, van den Oord, Verhulst, & Boomsma, 2003	Child Behaviour Checklist	Males[b] aged 3	Parent	0.54	0.13	0.33
		Females[b] aged 3		0.63	0.08	0.29
		Males[b] aged 7		0.46	0.26	0.28
		Females[b] aged 7		0.34	0.35	0.31
Boomsma, van Beijsterveldt, & Hudziak, 2005	Child Behaviour Checklist	Males & Females[a] aged 3	Mother & Father common phenotype	0.76	0.00	0.24
		Males & Females[a] aged 5		0.60	0.16	0.24
		Males & Females[a] aged 7		0.67	0.00	0.33
		Males[b] aged 10		0.60	0.05	0.35
		Females[b] aged 10		0.53	0.20	0.27
		Males & Females[a] aged 12		0.48	0.18	0.34

[a] No evidence for sex effects; [b] Significant sex effects

Initial inspection of the content presented in the table reveals two interesting facts. First, there is much variation in the estimated heritability between studies and it is evident that a simple average across these fails to satisfactorily summarise the findings. Rather, quantifying genetic and environmental influences on depression invariably involves deciphering the effects of age and sex, and methodological artefacts, such as the informant, on these estimates, and these have been explored extensively. As age and sex are clearly important to aetiology, these may offer explanations to the epidemiological trends described in Chapter 1, and will be focussed on specifically in this section. A second characteristic of twin studies is that the majority of studies have utilised questionnaire measures of depression including those which assess general internalising symptoms or those developed specifically for depression. Thus most studies are concerned with examining symptoms in the normal range and in fact only one study has reported findings from a clinically recruited sample (Glowinski, Madden, Bucholz, Lynskey, & Heath, 2003). Several studies have estimated group heritability, referring to genetic influences in extreme scoring individuals selected from the normal range. Whilst the identification of high scorers does not necessarily indicate clinical diagnosis, these findings may contribute somewhat to the resolution of the dimension versus categorical approach outlined in Chapter 1. Findings from these 'extreme' scores will be discussed below in a separate section to those estimated from the normal range.

Age effects

Cross-study comparisons of the different aged samples are generally suggestive of larger genetic effects in adolescents than in children. This trend is supported to some degree by the findings from several studies that have stratified their analyses according to age, and tested for statistically significant differences in estimated heritability between older and younger groups (Thapar & McGuffin, 1994; Hewitt et al, 1992; Eley & Stevenson, 1999; Silberg et al, 1999; Silberg et al, 2001; Rice et al, 2002; Scourfield

et al, 2003). These studies indicate developmental changes in the size of genetic effects during the transition from childhood to adolescence such that genes may become increasingly important during adolescence whereas shared environmental factors show a corresponding decrease. However there are at least three reasons why these conclusions may be premature. First it is unclear whether age-related changes differ between males and females. Two studies have reported larger genetic effects in adolescent females (Hewitt et al, 1992; Silberg et al, 1999; Silberg et al, 2001) whilst a third study found increases in adolescent males only (Eley & Stevenson, 1999). In a fourth study, greater genetic effects were demonstrated in both males and females, but the increase was marginally larger among females (Scourfield et al, 2003). These findings emphasise that age-related changes should be considered in the context of sex differences.

A second reason for casting doubt to these conclusions is that there is some difficulty reconciling these age trends with findings of substantial genetic influences in early childhood (54-76% at 3 years) compared to middle childhood (34-48% between 7-12 years), reported by two studies (Boosma et al, 2005; van der Valk et al, 2003). Furthermore there are also decreasing genetic effects over time during adolescence (a^2 = 48% at wave 1; a^2 = 22% at wave 2: O'Connor et al, 1998a, 1998b). Thus it would appear from these findings that the changes in heritability and shared environment are anything but linear across development, and may even reflect a u-shaped curve.

Finally, studies examining extreme scoring individuals have reported an opposite trend of effects, whereby genetic influences become smaller and shared environmental factors larger in adolescent high-scorers (e.g. Deater-Deckard et al, 1997; Eley, 1997; Gjone et al, 1996; Rice et al, 2002). Thus different patterns of results may characterise severe populations. Far from providing any simple answers, these seemingly discrepant findings with respect to age effects clearly point to additional lines of research.

Whilst cross-sectional comparisons of genetic and environmental influences across age groups have provided useful insights into age-related changes, another method for studying developmental differences is to examine the genetic contributions towards continuity and change of symptoms across different time-points. That is, longitudinal twin data allows an estimation of the extent to which the same genetic and environmental factors are important to depression symptoms at two different time-points (continuity) and whether there are new genetic and environmental factors in operation at the later time-point (change). Such studies are informative with respect to developmental processes unfolding over time and form a parallel line of enquiry to age differences described previously.

Two studies utilising this design have examined the causes of continuity and change within adolescence, finding that whereas genetic factors contribute to continuity over a period of two to three years, new environmental effects at the second time-point were responsible for change (O'Connor et al, 1998b; Silberg et al, 1999). Another study with a wider age range including both child and adolescent twins (5-14 years) reported a different pattern of results (Scourfield et al, 2003). Over a three year period, new genetic influences emerged at time 2 but shared and some non-shared environmental factors remained stable. Thus in this study, genes contributed towards change whilst the environment was the main source of continuity. Using a younger aged sample that spanned early to middle childhood, a fourth study demonstrated that although some genetic influences persisted between ages 3 and 7, thus contributing to stability, there were also 'new' genetic factors specific to each age (van der Valk et al, 2003). It is not immediately obvious why these differences exist between these studies. They may be due to methodological artefacts, such as the measure used to assess depression, the informant or rater, sex composition of the sample or length of follow-up. However a more intriguing alternative is that there are genuine differences between the distinct

developmental transition periods assessed in each study (early childhood to middle childhood, middle childhood to adolescence or within adolescence) which involve physiological, cognitive, social or emotional changes. These changes in turn may be driven by developmentally-sensitive aetiological influences. The possibility that in addition to 'stable' genetic factors, new genes can also be 'switched on' at different stages to account for these changes is certainly worthy of further investigation.

Sex effects

Studies examining sex differences typically stratify their analyses according to gender, to estimate differential heritabilities in the two groups. Statistical comparisons between models allowing for differences between males and females in genetic effects, with models equating these indices across sex, are used to establish significant sex differences. Reviewing findings across studies again yields inconsistent results. Four studies suggest greater genetic effects among adolescent females (Boomsma et al, 2000; Jacobson & Rowe, 1999; Silberg et al, 1999; Scourfield et al, 2001) whilst two others reported larger estimates in adolescent males (Rice et al, 2002; Eley & Stevenson, 1999). In children, there is some consensus that females show larger genetic effects (Eley & Stevenson, 1999; Scourfield et al, 2003; Happonen et al, 2002; van der Valk et al, 2003) but this has not always been replicated (Hewitt et al, 1992; van der Valk et al, 2003). Yet still other studies have found no sex differences in either age group (Bartels et al, 2003a, 2003b; Thapar & McGuffin, 1994; Gjone & Stevenson, 1997).

Sex differences can also be qualitative, that is, males and females may differ in the *types* of genetic and environmental factors contributing towards depression symptoms. However the examination of these differences requires the use of opposite-sex twin pairs, who generally tend to be under-represented in many twin samples. As a result, no studies to date have reported such differences. Together these studies provide only

modest evidence of sex differences in the heritability of depression. Whilst some studies reflect more complex interactions with age, the direction of these effects remains frustratingly unclear, reinforcing a need for further empirical clarification.

Extreme-scoring individuals

There are now at least 6 papers reporting on genetic and environmental influences of extreme depression (see Table 2.1), where 1 of these has analysed clinically significant data (Glowinski et al, 2003) and the remaining 5 have assessed high scores on measures of depression (Deater-Deckard et al, 1997; Eley, 1997; Gjone et al, 1996; Rende et al, 1993; Rice et al, 2002). Of note, two of these have used partially overlapping samples (Rende et al, 1993; Deater-Deckard et al, 1997). Analyses of extreme-scoring individuals prove valuable in the extent to which they may implicate aetiological continuity (or discontinuity) between depression in the normal range and those exhibiting more severe forms of the phenotype. Demonstrating that there are no significant differences in genetic and environmental factors between normal and extreme 'scorers' lends support to the notion that depression is a continuum.

Results of the analyses of extreme-scoring individuals, that is, those selected from high-scores on a continuous measure, are reasonably consistent in suggesting that compared with individuals scoring in the normal range there are non-significant trends for genetic effects to be lower whilst shared environmental factors increase in importance (Deater-Deckard et al, 1997; Eley, 1997; Rende et al, 1993; Rice et al, 2002). Of note, the study conducted by Rice and colleagues only found this pattern of effects among adolescent self-reported data; for parent-reported adolescent data, genetic and shared environmental effects estimated at the extremes were comparable to those operating in the normal range. Unexpectedly, this pattern did not apply to the clinically significant sample, which demonstrated comparable heritability and shared environmental effects

to normal-ranged individuals. Thus there appear to be discrepancies between severe populations selected from the extreme end of normal individuals, and clinical populations. Given that this latter study constitutes only one of its kind, further replications will be needed before these differences are interpreted.

The papers analysing extreme groups also hint at age-related trends, such that genetic influences are sizably larger and shared environmental effects smaller in high-scoring children (Rice et al, 2003). Another study also demonstrated that whilst non-significant decreases in genetic effects and increases in shared environmental effects characterised older high-scoring individuals (12-15 years), in the younger group (5-6 and 8-9 years) high scorers showed significantly larger genetic but negligible shared environmental effects (Gjone et al, 1996). Together these results suggest that aetiological influences involved in the development of severe depression are somewhat different between childhood and adolescence. Only two of these studies (Gjone et al, 1996; Rice et al, 2002) considered sex differences in group heritability and shared environmental effects, with neither study reporting significant differences. Thus at present until further study, aetiological mechanisms operating at the extremes may be similar for girls and boys.

2.2.2.3. Adoption Designs

The adoption design offers yet another method of disentangling genetic from environmental influences, drawing upon the differential relationships that occur within adoptive families and non-adoptive biological families. In adoptive families the adoptee will share rearing environments, but not their genes with other family members. In contrast, individuals from non-adoptive biological families have both their rearing environment and 50% of their segregating genes in common with other family members. Similar to the twin design, correlations between dyads within these two family-types can be re-expressed to reflect the different degree of shared genetic and

environmental components. The comparison in correlations is then used to yield estimates of genetic and shared environmental influence. A noteworthy feature of this design is that the estimate of shared environment is directly inferred from the relationship between adopted family members, rather than as the non-genetic residual variance contributing to twin similarity in the twin design.

Only two published studies examining depressive symptoms in adopted children and adolescents have been reported (Eley, Deater-Deckard, Fombonne, Fulker, & Plomin, 1998; van den Oord, Boomsma, & Verhulst, 1994). Results have been in stark contrast to those suggested by twin studies, with findings of negligible genetic and shared environmental effects. In the earlier study, correlations between biologically related siblings adopted in the same family were compared with correlations between biologically unrelated siblings also adopted in the same family on the Internalising scale of the Child Behaviour Checklist (van den Oord et al, 1994). Children were aged 10 to 15 years. Comparisons in correlations across sibling-types were similar and somewhat smaller among biological adoptees, suggesting virtually no genetic effects. However moderate shared environmental effects and substantial contributions by the non-shared environment were revealed.

The second study used parallel parent-offspring and sibling designs within their adoption study of middle childhood (9-12 years) (Eley et al, 1998). Mother-offspring resemblance was first compared among biological, adoptive and non-adoptive biological control parents with their children through correlations between depression symptoms in the children and neuroticism in the mothers. Secondly sibling correlations in adoptive families and in non-adoptive biological control families were compared. Both designs suggested negligible genetic influences, small shared environmental effects but substantial non-shared environment.

It is as yet unclear why the findings from adoption studies are at odds with the conclusions reached in twin studies. In both samples, the offspring were fairly young (10-15 and 9-12) and genetic effects have not always been consistently found in this age group. A second possibility is that the genetic effects demonstrated among twins are expressed only in interplay with exposure to specific environments, a topic explored in a subsequent section of this chapter. Whilst there are no obvious explanations for these conflicting results, at the very least the results from adoption studies should heed caution in the interpretation of findings from twin studies, and emphasises the need for further work in middle childhood.

2.2.3. Studies of Genetic risk mechanisms

Until recently genetic and environmental factors were inaccurately represented in most quantitative genetic designs as having additive and independent effects on measured phenotypes. This was encouraged in part by a shortage of analytical frameworks able to easily assess correlations and interactions between genetic and environmental factors, and as a result such effects, if present were subsumed within main effects. Thus gene-environment correlations (rG-E), which occur when there are genetic influences on environmental risk exposure, will often be included within the genetic term in a traditional twin analysis. Similarly gene-environment interactions (GxE), which refer to genetic influences on susceptibility to environmental risks, will be incorprorated within the main genetic or non-shared environment estimate depending on whether the environmental risk factor is of a shared or non-shared source. Whilst neither form of interplay between genetic and environmental factors is readily interpretable in the basic twin design, this does not imply that they do not exist. To the contrary, positive findings have been reported in quantitative and more recently, molecular genetic studies. Although most of the seminal work underpinning support for these processes was conducted in adult samples, both processes have been heralded as having tremendous

potential for understanding *how* genetic effects are expressed as risk mechanisms in younger populations too (Rutter, 2003). This successful demonstration of their importance has relied partly on several methodological advances in quantitative genetic analyses and these are reviewed after discussion of the conceptual basis of each process.

2.2.3.1. Gene-environment correlations

Statistically, correlations between genes and the environment arise when genotypic frequencies, that is, the number of individuals carrying a particular genotype, are not randomly distributed across levels of environmental risk. Rather there are more individuals of a certain genotype represented at a particular environmental stratum. Conceptually this indicates that there are genetic influences on exposure to an environmental condition. This influence can be manifested in one of three contexts involving passive, evocative or active processes (Scarr & McCartney, 1983). Passive gene-environment correlations come about due to the sharing in biological families of both genes and environment. Thus it occurs when the effects of parental genotype are related to the family environments their children are exposed to. For example offspring of depressed mothers are likely to receive both a genetic predisposition towards this condition and the environmental effects of a depressogenic parenting style, which may characterise the social interaction styles of these mothers.

Evocative gene-environment correlation refers to the genetic propensity of some individuals to elicit or evoke certain reactions from others. These effects may be mediated through intermediate factors, such as temperament or cognitive style factors. Thus infants who cry easily or show irritability may be more likely to elicit negative reactions from caregivers, which have implications for parenting style. Finally, active gene-environment correlation occurs when individuals select, create and modify their environmental experiences based on particular genetically mediated dispositions.

Behaviourally inhibited or shy individuals may be less likely to seek out friendships and social contacts and instead choose to engage in solitary play, thus ultimately influencing their socio-emotional development.

Support for genetic influences on environmental risk exposure is strong. Most of this evidence is longstanding, derived from earlier work with adult samples through quantitative genetic designs. These have shown that many aspects of the environment, for example stressors, not only aggregate in families (e.g. McGuffin, Katz & Bebbington, 1988) but moreover are genetically influenced (e.g. Kendler & Karkowski-Shuman, 1997). However what is pertinent to the study of risk mechanisms on depression is not that genes influence environments per se, but that genetic vulnerability involved in depression, is expressed through exposure towards high-risk environments. In other words, genetic risks for depression should overlap to some extent with genetic influences on environmental exposure. This has been widely reported in adolescent studies where genetic risks for depression symptoms also contribute to negative parenting styles (Pike, McGuire, Hetherington, Reiss, & Plomin, 1996) and to negative life events (Eaves, Silberg, & Erkanli, 2003; Rice, Harold, & Thapar, 2003; Silberg et al., 1999; Thapar, Harold & McGuffin, 1998). Moreover, it has been suggested, that processes of gene-environment correlation, particularly active processes may become more prominent during adolescent years, thus accounting for age-related increases in this age range (Silberg et al, 1999; Rice et al, 2003) and possibly some of the new genetic influences, which purportedly emerge (Scourfield et al, 2003). Examination of these processes in childhood has been limited, partly as a result of inconsistent findings of genetic effects in younger samples.

In summary, gene-environment correlations, which can be differentiated according to a taxonomy of three types, represents several paths by which genes may be expressed through psychosocial processes. These processes have been used to account for the

increased genetic effects reported in adolescence. Additionally they have also been proposed as an explanation of why adoptee samples typically show lesser genetic effects. That is, individuals who have been adopted may not necessarily be exposed simultaneously to both genetic risks and correlated adversity in their rearing environments.

2.2.3.2. Gene-environment interactions

Interactions refer to the differential effect of one variable at differing levels of another variable. As such gene-environment interactions arise when the effects of an environmental risk factor vary as a function of genetic risk, or when genetic risks are expressed only in the presence of an environmental stressor. Thus, either the impact of the environment is moderated by the individual's genotype or genetic risks are moderated by the presence of an environmental condition. In terms of risk mechanisms, interactions refer to genetic influences on reactivity towards the environment.

Demonstrating gene-environment interactions in depression has proven difficult, given that more statistical power is required to detect interactions than main effects. Thus, large samples are essential. Nevertheless, this has not prevented a gradual accumulation of studies dedicated towards finding these effects, although similar to studies of gene-environment correlation, most of the pioneering work was conducted within adult samples (e.g. Kender et al, 1995) with a more recent focus on adolescent populations.

Family designs afford one possibility for exploring interactions. Exemplifying this approach, one study used a composite index of parental familial vulnerability to anxiety, depression and neuroticism to predict depressive outcomes in their offspring (Eley et al., 2004a). This index was thought to reflect shared genes among family members. A significant interaction emerged between this composite and parental lack of educational qualifications on self-reported depression symptoms in the adolescent offspring. This

finding may be attributed to indications that parental education levels are predictive of maladaptive parent-child relationships (Napolitano & Eley, 2004), which then act as the moderating environmental stressor. Whilst results from this study are thought-provoking in terms of identifying specific pathways to adolescent depression, they are simultaneously limited by a failure to discount the alternative suggestion that the familial composite reflects shared environmental influences rather than shared genes among family members. As such the interaction may represent an environment-environment interaction rather than a gene-environment interaction.

Variations of the twin design have permitted the use of two different but specific tests of gene-environment interaction as demonstrated in one study of adolescent females (Silberg, Rutter, Neale, & Eaves, 2001). This showed firstly that certain environmental stressors, such as negative life events exacerbated the genetic effects on depression and anxiety symptoms as reported by the sample. Secondly individuals at genetic-risk for anxiety and depression as indexed by the presence of parental emotional disorders were also more likely to exhibit depressive symptoms following recent negative life events. Thus the first test represents an environmental moderation of genetic risk, whereas the second shows a genetic moderation of environmental risk.

An important point to consider in studies of interactions is whether there are confounding effects due to gene-environment correlation. Often, what are recognised by default as interactions may also be interpreted as genetic risks for depression, which lead to increased social adversity. In fact, the validity of interaction effects is premised on the assumption that genotypes are randomly distributed over the range of environmental conditions (Eaves et al, 2003). This can be easily violated when individuals with a certain genotype are more likely to be exposed to a particular environmental condition or when the environmental measure is influenced by genes also contributing to the phenotype. In other words, whilst testing for interactions, it must be

very clear that the environmental variable examined is not influenced by genes that are also associated with behavioural outcomes. Should this be the case, this may signify a gene-environment correlation on the phenotype rather than an interaction.

However it is likely that gene-environment correlations co-exist with interactions on many aspects of environmental risk. Many studies have indeed demonstrated that the same environmental risk (e.g. life events) is involved in both processes of interplay (e.g. Silberg et al, 1999; Silberg et al, 2001). Thus instead of finding measures of the environment that are free from genetic influence, designs should be developed that simultaneously assess and differentiate interactions from correlations (Eaves et al., 2003; Purcell, 2002). A study addressing both processes on adolescent depression reported several distinct pathways (Eaves et al, 2003). First genes that were shared between prepubertal anxiety and later depression influenced exposure to negative life events (correlation). Second, these life events influenced depression directly (main effects) but also interacted with genetic factors on the phenotype (interaction). These interactions occurred between genetic factors previously implicated in the exposure to life events (interaction in the presence of correlation) and genetic factors that were specific to depression (interaction in the absence of correlation). As this study neatly demonstrates, interactions and correlations not only represent distinct processes in the development of depression but may occur at different stages. For instance genetic risks on the phenotype may be involved in the creation of an environmental risk, whose occurrence then exacerbates genetic effects on the outcome.

These preliminary analyses of the combined effects of gene-environment correlations and interactions on depression are clearly in need of further examination and replication across a wider range of social stressors. However they lay the foundation for understanding how genetic and environmental risk factors may be mediated through intermediate processes which eventuate in symptoms. This paves the way for the second

topic of this chapter, cognitive theories of depression, which focus on intermediate processes governing the transition from liability to symptoms.

2.3. Cognitive Approaches

2.3.1. Key Concepts

Cognitive models of depression focus on risk factors defined and measured at the level of information-processing or thoughts. Many of these are considered top-down accounts of psychopathology, given that they begin with an individual's behavioural experiences and work backwards, seeking psychological mechanisms to explain patterns of behaviours (Pennington, 2002). Psychological mechanisms include 'surface level' cognitions, which refer to thoughts that are accessible to conscious awareness such as automatic thoughts and self-statements; 'deep level' cognitions, which are trait-like and stable characteristics, such as core beliefs and assumptions that affect an individual's behaviour through unconscious processes; and lastly more subtle aspects of information processing, such as attention or memory processes, which are automatic and unconscious (Segal & Swallow, 1994). According to different models, variation in a particular cognitive factor contributes towards individual susceptibility to depression.

Two of the most influential cognitive theories of depression have focussed on the role of 'deep level' cognitions (Garber & Robinson, 1997). Beck's theory of depression (Beck, 1967), originally derived through extensive therapeutic experience with patients, has three central constructs: maladaptive schemas and dysfunctional attitudes, cognitive distortions and a cognitive triad of negative thoughts. In brief, schemas are cognitive structures which represent all information in the world into psychologically relevant facets. According to the theory, individuals with depression possess maladaptive schemas, which involve themes of personal deficiency, self blame and negative expectations, and which are manifested and indexed through the presence of

dysfunctional attitudes. These maladaptive representations may be formed through a combination of adverse childhood events as well as an individual's tendency to engage in systematic errors in thinking or cognitive distortions, such as overgeneralisation, selective abstraction, magnification and minimisation, personalisation, and arbitrary inference. Over time, such maladaptive schemas may give rise to a distorted (negative) view of the self, the world and the future, and it is this 'cognitive triad' of negative thinking which confers vulnerability towards depression. Support for the presence of dysfunctional attitudes and a negative cognitive triad in depressed individuals including children (e.g. Robinson, Garber, Hilsman, 1995) has been documented. However a lingering uncertainty plaguing the theory is whether these cognitive factors precede depressive symptoms, co-occur with or follow them. As a result of the circularity of the theory's arguments, more contemporary views have shifted their focus from a predominantly causal model of depression to one which 'maintains' depressed mood. This has had far-reaching implications for the application of the theory towards the development of cognitive-behavioural therapies. As a result the *theoretical* emphasis of Beck's seminal work has essentially been replaced with a more explicit *clinical* orientation.

A second cognitive model of depression, which has also received widespread empirical attention and which is the main cognitive theory examined in this thesis, is the reformulated helplessness theory (Abramson, Seligman, & Teasdale, 1978). This theory focuses on the role of cognitive style as a predisposing factor of depression. Specifically individuals who attribute negative events to internal (directed to the self), stable (likely to persist over time) and global (likely to affect many aspects of life) causes, and positive events to external, unstable and specific causes, are at-risk for depression. More recent elaborations of the theory have postulated that this cognitive vulnerability is expressed only in the presence of stressful life events (Alloy, Abramson, Metalsky, &

Hartlage, 1988), and that psychological constructs such as hopelessness and self-esteem mediate its risk effects on depression (Abramson, Metalsky, & Alloy, 1989).

The research agenda of attributional style has been shaped by two main issues. The first concerns the theory's central tenets, namely that attributions are *causally* related to depression, and moreover that this association is moderated by negative life events. Unlike Beck's theory, there has been rather more support cited for a causal role. A second area of burgeoning interest is the developmental trajectory and aetiological origins of attributional style. Related to this, are specific questions as to *when* it is acquired and becomes operational as a vulnerability factor of depression, and secondly on the identity of risk factors contributing to its development and the nature of these risks on depression. Each of these areas is reviewed in turn.

2.3.2. The role of attributional style

There has been a wealth of studies reporting robust associations between negative attributions and depressive symptoms (Gladstone & Kaslow, 1995). However these have largely been restricted to cross-sectional studies, which are ill equipped to test the stronger clause of the theory, notably that there is a causal pathway between them. Empirical support for this has been explored extensively using various different study designs with mixed results. Behavioural high-risk predictive designs, which are based on inferences of causality from the temporal relationship between variables, have generally reported that individuals who are non-depressed but who manifest negative cognitions at baseline are more likely to develop depression compared with control counterparts at subsequent time-points (Alloy et al., 1999). Studies examining the offspring of depressed parents, and who are at risk as a result of genetic and environmentally transmitted vulnerabilities, show that these children are more likely to report negative attributions compared with the children of control parents. Thus, these

suggest an overlap between risk for depression and cognitive style even when controlling for current levels and past history of depression symptoms (Garber & Robinson, 1997). Finally the 'remitted' depression design, which compares the cognitive styles of currently depressed individuals with those of formerly depressed individuals, has been less supportive of a causal relationship. If cognitive style is indeed a predisposing 'trait' factor for depression, one would expect negative cognitions to be present even during symptom-absent periods. However this has not been consistently reported, with some studies showing that negative cognitions only occur during depressive episodes (Hamilton & Abramson, 1983) and others where individuals in remittance continue to report a negative cognitive style (Eaves & Rush, 1984).

One interpretation of these results is that attributional style may also represent a 'scar' effect, a consequence of previous episodes of depression. Indeed, there is evidence to show that although changes in attributions initially precede those of depression symptoms subsequently increasing levels of depressive symptoms also predict increasingly negative attributional styles (Garber, Keiley, & Martin, 2002; Nolen-Hoeksema, Girgus, & Seligman, 1992). Thus there may be a reciprocal and 'interlocking' relationship between the trajectories of attributional style and depression, such that a viscous circle is created, where the effects of one exacerbate the other. Alternatively both attributional style and depression may reflect a common biological or genetically based vulnerability (Dahl & Ryan, 1996), such that attributional style is an extended phenotype or 'state' factor of depression. Exploring each of these hypotheses has clear implications as to whether attributional style reflects a causal risk factor of depression, or if it is a concomitant manifestation of the mood-related phenotype or a consequence of previous bouts of symptomatology. As these roles are not mutually exclusive, it may comprise all three.

Recent support for the diathesis-stress component of the theory, which postulates an interaction between negative life events and attributional style to influence depression. has generally reported in favour of the hypothesis (e.g. Hankin, Abramson, & Siler. 2001). Thus attributional style may play a latent risk effect on depression that is only elicited in the face of stress. However it has also been noted that this interaction is often not documented in younger aged samples (e.g. Abela, 2001; Turner & Cole, 1994), leading to the intriguing suggestion that the moderating effect of negative stressors on the relationship between attributional style and depression emerges only during particular stages of development. The hypothesised developmental trajectory of attributional style and its aetiological origins are discussed in the next section.

2.3.3. Developmental course and origins

As with Beck's theory, it has been hypothesised that attributional style is also acquired during childhood, through the occurrence of negative events and the feedback the child receives regarding the causes and consequences of such events. However this cognitive factor is also thought not to become operational until the transition from late childhood to early adolescence, following the maturation of several areas of cognition including abstract reasoning and formal operational thought, which may underpin its functioning (Turner & Cole, 1994). Given its emergence during adolescence, it has been suggested that attributional style may explain the observed age-related increases in depression.

Growing support for these developmental hypotheses has been demonstrated through cross-sectional comparisons of the predictive nature of the relationships between attributional style, negative life events and depression in different age groups (e.g. Cole & Turner, Jr., 1993; Abela, 2001). Interactions between life events and attributional style on depression symptoms have been documented in seventh grade children (13 years) but not third grade children (9 years) (Abela, 2001). Furthermore in younger

children, attributional style mediates the effects of negative events on depressive symptoms rather than playing a moderating effect (Cole & Turner, 1993). Whilst these changes are likely to reflect a continuous trajectory of development, they also imply the operation of developmentally-sensitive factors which come 'online' in adolescence. Thus developmental context should be a key consideration when exploring the nature of attributional style as a vulnerability influence on depression.

Related to the developmental course of attributional style is interest in the origins and early predictors of this cognitive factor. To date, there has been comparatively little research on this, leading to some criticism that attributional style may lack explanatory power as a theoretical model of depression (Pennington, 2003). A few studies which have examined psychosocial factors of attributional style have shown the importance of maternal depression and negative attributions, negative parental practices of control and discipline, and childhood negative events (Garber & Flynn, 2001; Murray, Woolgar, Cooper, & Hipwell, 2001). Typically these factors have been depicted as environmentally mediated risks on attributional style. For example, high correlations between maternal cognitive style and child cognitive style may be due to social learning processes, particularly modelling and feedback (Alloy et al, 2001). Similarly, the relationship between maternal depression and negative attributional style is thought to be mediated by the depressogenic rearing environments that such children may be exposed to (Murray et al, 2001). Finally negative parental practices and stressful life events have traditionally been conceptualised as representing dimensions of social risk (Goodyer, 1990; Rapee, 2001).

Whilst it is very likely that socially mediated risks are involved in the creation of attributional style, an alternative explanation that has received lesser attention is the role of hereditary factors. That is, genes may also contribute to the development of a negative attributional style. Indeed higher concordances among adult monozygotic

(MZ) compared with dizygotic (DZ) twins have been reported, suggesting genetic effects (Schulman, Keith, & Seligman, 1993). However as MZ twin correlations were less than 1.0, these results also support significant environmental involvement. Thus rather than negating the importance of the environment, a combination of both risks on attributional style is likely. A second line of argument for genetic effects paradoxically, is the findings of associations between parenting styles and child attributional styles. As reviewed previously there may be genetic effects on aspects of the parent-child relationship (e.g. Pike et al, 1996) and that these genetic influences may overlap with those involved in phenotypic outcomes in the offspring. As these processes have been found to be important to emotional symptoms, the possibility that the association between specific parenting styles and negative attributional style also reflects these gene-environment correlations is considerable.

If genetic effects are indeed important to the formation of attributional style this will have implications for models of depression. Although there is consistent evidence that genetic influences contribute to adolescent depression, what is less clear is how these risk effects are expressed through psychosocial pathways to influence phenotypic vulnerability. One possibility is that cognitive factors, such as attributional style reflect distal genetic vulnerability associated with depression. Thus negative cognitions observed in offspring of mothers with depression may be phenotypic manifestations of the genetic diathesis for depression (e.g. emotional reactivity) transmitted between generations (Murray et al, 2001). A similar line of reasoning has been adopted by another theoretical model, such that genetic risks for neuroticism (and therefore depression) operate to increase exposure to negative events over time (Hankin & Abramson, 2001). Such negative events contribute incrementally to the formation of a negative attributional style, which during adolescence interacts with other stressors to confer vulnerability to depression. According to both hypotheses, genetic effects are

expected to account for some of the association between attributional style and depression. However given that environmental influences may act as distal vulnerability (social learning, negative events) influencing the development of negative attributions (and therefore depression), the association could also reflect socially mediated risks. To date, these genetic and socially driven hypotheses on attributional style and its association with depression have not been explored. Preliminary speculations on how cognitive risk factors such as attributional style partake within genetic and social risk mechanisms to influence depression, is explored further in the next section.

2.4. Psychosocial Approaches

2.4.1. Key Concepts

The possibility that environmental risks contribute to depression remains almost undisputed by the majority of theories of depression. Even biologically-driven theories, such as genetic approaches have demonstrated the main effects of environmental contributions and more recently, their interplay with genes on depression. Unlike behavioural geneticists who define the environment primarily according to whether they increase resemblance between family members (shared environment) or contribute to differences between individuals (non-shared environment), social theories are concerned with identifying *specific* aspects of the environment and the mechanisms by which they influence depression. Earlier investigations of environmental factors on depression were guided principally by concepts gleaned through clinical assessments, and tended to be non-experimental and atheoretical. These emphasised general notions of 'change' and 'stress', which were involved in the genesis of a wide range of psychiatric conditions (Holmes & Rahe, 1967; Lazarus, 1966). In the 1970's a transition from identifying 'general' stressors towards more specific associations between

different *types* of stress and symptoms occurred, leading to a search for risk factors with differential roles in accounting for predisposition (Brown & Harris, 1989).

A more recent shift in the field, however has been to move even beyond such 'univariate' findings to exploring the combined effect of multiple social factors on phenotypic outcomes. Most models have focussed primarily on disentangling the moderational and mediational relationships, which govern the inter-relationships among different risk factors. However with advances in multidisciplinary research, the integration of genetic-biological factors and cognitive-interpersonal factors within these explanations has been advocated, in addition to representing these dynamic risk processes within a developmental perspective (e.g. Goodman & Gotlib, 1999).

The remainder of this section is divided into two sub-sections. The first examines the taxonomy of different types of stressors that has emerged in earlier studies of social factors, whilst the second traces the theoretical progression from simple associations between depression and social risk to more complex integrated models.

2.4.2. Specific social risk factors

One of the first distinctions made between different sources of stress influencing depression was 'loss' and 'threat'. It was postulated that loss events played a crucial role in depression whereas threat events were related to anxiety (Finlay-Jones & Brown, 1981). This distinction, which has been demonstrated in adult samples, has also been replicated to some extent in children (e.g. Eley & Stevenson, 2000). Although these labels offer great heuristic value towards the identification of relevant social factors, they have also been criticised on the basis that they are vague and over-inclusive. For example loss refers to both tangible events, such as bereavement, and psychological states, such as loss of identity following the birth of a sibling. Given that almost any

traumatic event can be re-defined as a loss, this has cast doubts on the validity of these terms, leading to alternative distinctions.

One suggestion has been to define vulnerability at the level of the 'process' rather than at the 'variable' (Rutter, 1990). Instead of relying on 'surface' characteristics, which are often ambiguous, this approach considers distinctions that are based on the specific *roles* of stressors rather than global themes. To this end 'provoking agents' and 'vulnerability factors' have been identified. Provoking factors are discrete events whose occurrences precipitate symptoms whilst vulnerability factors or chronic difficulties refer to background sources of ongoing stress, which incrementally increase risks to depression in the presence of other risk factors. This distinction has led to the identification of specific risk factors, falling into these two categories.

Negative life events are defined as major changes in the external environment, such as death of a close family member or failing an exam, and have been demonstrated to precede depressive symptoms (Brown & Harris, 1989). As such they have been thought to represent provoking factors. Several age-normative stressors, such as aspects of the family environment, parent-child relationships and school-related stressors have been proposed as vulnerability factors of depression. Family environmental factors have included parents' mental (presence of psychopathology), social (parental relationships and life events) and occupational functioning (SES, parental educational level) (Goodyer, 1990), whilst parent-child relationships refer to early attachment and child-rearing practices of control or rejection. School-related stressors have included academic achievements and peer relationships (Goodyer, Wright, & Altham, 1989; Goodyer, Wright, & Altham, 1990).

Whilst the categorisation of social risk factors into provoking events and background factors has been widely endorsed, it has also been recognised that it is over-simplistic if

rigidly applied. Provoking agents, such as life events are often interspersed within a web of contextual factors, such as parental psychopathology (Goodyer, 1990). These synergistic effects, which may occur over time, need to be taken into account by current social models of depression. This has led to the development of integrated life stress and interpersonal models, which consist of various different risk factors and their inter-relationships (e.g. Goodman & Gotlib, 1999) and are discussed next.

2.4.3. Integrated life stress and interpersonal models

The aim of most integrated models is to address the inter-relationships between psychosocial risk variables and the mechanisms by which these are translated into vulnerability. Given that many life events and chronic stressors associated with child and adolescent depression are embedded within the family context, a starting point for many models are psychosocial risk processes occurring in the family environment. Findings from family-process models confirm that the routes between social risks and developmental outcomes are far from linear but instead involve interactions between different sources of risk, such that the presence of one factor (e.g. bereavement during childhood) exacerbates the effects of others (e.g. negative life events); and mediation, where the effects of one social factor (e.g. marital conflict) are transmitted through other variables carrying more proximal risks (e.g. negative parenting) (Goodyer, 1990). In relation to depressive outcomes, the literature is replete with examples of pathways involving mediation, with fewer studies to have examined interactions.

An example of a study examining mediation or indirect paths showed that parental neuroticism was associated with a variety of deficits in occupational and social functioning, such as lower levels of parental education and income, more negative life events, avoidant and emotion-focused coping skills and parenting practices which were less supportive and structured (Ellenbogen & Hodgins, 2004). Insofar that many of

these variables were also significant predictors of child internalising symptoms, findings of this study were consistent with the suggestion that some of these variables mediated the effects of parental neuroticism on outcome. Using similar analytic techniques, other studies have reported that facets of marital relationships, such as conflict and attachment security between spouses mediate the effects of parental dysphoria on child outcomes (Cummings, Keller, & Davies, 2005; Burt et al., 2005).

Although it is tempting to conclude that parental emotional and mental functioning contributes to child internalising symptoms, indirectly through the creation of more proximal stressors in the environment, there may be two reasons why this interpretation is premature. First, social risk factors often show reciprocal relationships with one another. Results from another study demonstrated the reverse pattern of effects to those described above, such that the impact of parental relationship and marital problems on child emotional symptoms were mediated entirely through maternal anxiety and depression (Spence, Najman, Bor, O'Callaghan, & Williams, 2002). Thus stressors acted indirectly on mother's mental health to influence anxiety and depression in their offspring. Whilst bi-directional effects are likely to exist between parental stress indices and their emotional well-being, an added strength of this latter study was that data were collected longitudinally. In this instance the temporal ordering of variables lends extra justification for inferences of the direction of mediating effects.

A second issue that can also challenge existing interpretations of results is genetic transmission. Many findings reported from these models neglect to consider this alternative explanation. Given that many aspects of the social environment are genetically influenced (Plomin & Bergeman, 1991), it is feasible that genetic effects associated with parental neuroticism are expressed through the creation of other social risks. In fact, in the study described previously, neuroticism reported by parents correlated positively with family history of major affective disorder, indicating that this

trait may reflect genetic risks on offspring (Ellenbodgen & Hodkins, 2004). Similarly, in examining the predictive effects of maternal anxiety and depression symptoms on child emotional behaviours (Spence et al, 2002), an elevated level of risk was documented among children who had experienced repeated exposure to maternal depression during early childhood (before the age of 5) and adolescence (age 14). Whilst this finding was attributed to the cumulative effects of maternal depression, a different interpretation is that the association reflects the greater genetic loading among adolescents whose mothers reported more severe forms of the phenotype.

Given that these alternative explanations cannot be discounted, genetic factors should be considered in integrated life stress and interpersonal models, although this has been rare in child and adolescent samples. Findings of genetic influences on environmental risk exposure have led some to challenge social causation hypotheses, arguing that 'pure' environmental effects associated with psychosocial risk factors may be reduced (Bergeman & Plomin, 1991). Although this has been disputed through claims that the origins of an environmental risk factor should not be confused with their impact (Rutter, Pickles, Murray, & Eaves, 2001), nevertheless the inclusion of genetically informative data into the examination of environmental risk variables can reduce the confounding effects between these two sources and may provide a more rigorous test of social mediation (e.g. Kim-Cohen, Moffitt, Taylor, Pawlby, & Caspi, 2005). Whilst there are concerns that the assumptions held by these approaches are logically flawed (e.g. (Purcell & Koenen, 2005), considering genetic risk mechanisms with psychosocial factors can also maximise the explanatory power of a phenotypic outcome through joint analysis of several variables (e.g. Kendler, Kessler, Neale, Heath, & Eaves, 1993).

Simultaneously to recognising the role of genetic factors within the context of psychosocial models, incorporating cognitive vulnerability factors can provide an even fuller picture of the aetiology of depression (Goodman & Gotlib, 1999). Cognitive

factors, such as attributional style may provide the intermediate mechanisms through which social (and possibly genetic) risks exert their effects on the phenotype. For example, the effects of negative parenting on depression were mediated through negative attributions (McGinn, Cukor, & Sanderson, 2005). Conversely, certain psychosocial risk factors, such as chronic stressors may also define the developmental origins of negative attributions. A slightly different mechanism governing the relationship between cognitive and psychosocial factors is that provoking social factors may provide the means through which cognitive vulnerability is expressed on the phenotype. In other words, cognitive factors such as negative attributional style are thought to interact with life events to effect depression symptoms (Alloy et al, 1999). Thus including cognitive factors within psychosocial explanations adds an intermediate process, through which psychosocial risks may be mediated through or interact with.

The examination of genetic and cognitive variables in the psychosocial context which includes mediational and interactive relationships between variables has begun to be examined in adult populations (e.g. Kendler et al, 1993) but with fewer attempts to extend these to child and adolescent models. Examining these risk processes in younger samples can contribute towards identifying developmentally-sensitive stressors and how these are expressed to influence depression symptoms.

2.5. Conclusions and Study Questions

2.5.1. Conclusions

Two main themes emerge from this brief review of behavioural genetic, cognitive and psychosocial theories. First it is evident that depression is a multifactorial phenotype. Although genetic, cognitive and psychosocial approaches each offer a unique perspective into the risk mechanisms underlying depression, varying at the *level* with which vulnerability is defined, it is clear that what is at first seen as rather disparate

approaches may in fact represent different pieces of the same puzzle. In other words, these theories may complement one another in explaining risk mechanisms of depression. Indeed, the more recent studies from each discipline have alluded to links between different 'levels' of risk factor, which have increased the explanatory power of how risk factors may be expressed. For example, processes of gene-environment interplay may implicate the role of intermediate processes in the expression of distal genetic and environmental risk. Similarly, attributional style may provide the intermediate mechanisms by which genetic and psychosocial risks are exerted. Conversely, identifying genetic and psychosocial influences on attributional style provides insight into the aetiological origins of this vulnerability factor and the nature of the risks that it poses for depression. Although many studies have begun this leap forward by considering inter-relationships between two 'levels' of risk factor, an even greater step may be to explore potential links between *multiple* domains of risk factor. This eclectic approach to understanding the development of psychopathology is a novel trend, and has been embraced by several conceptual models of depression (Hankin & Abramson, 2001) and anxiety (Rapee, 2001) although empirical testing of the links hypothesised by these models have been rather limited as yet.

A second theme concerns the role of developmental processes whereby all three approaches recognise the dynamic nature of these risk mechanisms, and that these may change across development. For example, genetic explanations may implicate increasing genetic effects and the possible emergence of new aetiological influences across developmental stages. Cognitive theories subscribe to a similar view that new vulnerabilities are expressed during adolescence, notably attributional style, after certain developmental milestones are reached. Although psychosocial theories have been less explicit about the role of social factors in accounting for developmental trends in depression symptoms, there is some indication that there are age-specific stressors, and

that adolescents may experience more stressful events and chronic stressors. Furthermore, such stressors may elicit latent cognitive or genetic vulnerabilities through interactive mechanisms during this period. Combining these different explanations for age-related changes may also be beneficial to understanding developmental risk mechanisms.

2.5.2. Study questions

Based upon the themes of the current Chapter and those of Chapter 1, this thesis sets out to understand the multifactorial aetiology of depression, and its developmental trajectory. Specifically, the role of genetic, cognitive and psychosocial risk factors on vulnerability to depression, and then their combined effects will be explored. Given that marked increases in the prevalence rates of depression is witnessed during adolescence, this developmental period will be the main focus for addressing vulnerability factors. However examining these processes in parallel during childhood offers an additional lens to view the development of depression unravelling over time.

Research questions progress from examining issues unique to each of the perspectives offered by genetic, cognitive and psychosocial theories towards their integrated and combined effects on vulnerability. There are 3 main sections. The first section (Chapters 4-5) examines the nature and expression of genetic risks on depression symptoms. Chapter 4 aims to replicate and clarify unresolved effects of age, sex, developmental change, on the genetic and environmental aetiology of depression, in addition to aetiological influences operating at extreme scoring individuals. Chapter 5 investigates the combined effects of genetic influences on risk exposure to negative life events and parental punitive discipline (gene-environment correlation) and on the susceptibility towards these risks (gene-environment interaction) during adolescence.

The next section (Chapter 6) focuses on attributional style as a possible cognitive marker of genetic influence on depression symptoms particularly during adolescence. This Chapter addresses the heritability of attributional style, and more interestingly, whether its association with adolescent depression reflects shared genetic and shared environmental effects. Parallel analyses targeting these questions are conducted in a child sample, allowing examination of any changes in the aetiology of this factor across development. The final aim of this Chapter is to address whether attributional style reflects a concomitant, causal or consequential effect on depression, given that this is critical to its validity as a predisposing factor.

The third section (Chapter 7) examines the role of psychosocial influences on depression. Beyond identifying specific social environmental predictors of depression symptoms in children and adolescents, the main aim is to address inter-relationships among risk factors and the mechanisms by which they are expressed. In addition the roles of attributional style and genetic factors are also incorporated into the analytical framework to assess the combined effects of different domains of putative risk factor.

Finally summaries of the findings from each Chapter with general limitations of the overall study are presented in Chapter 8. Tentative interpretations of these findings and how these may contribute towards a comprehensive model of the development of depression symptoms is speculated upon and the intricacies of the different pathways of this model discussed. This is followed by directions for future multidisciplinary work, which can further clarify the different aspects of such a model, and brief discussion of clinical implications.

Before these research questions are explored, Chapter 3 gives an overview of the methodology used in thesis, its principles and assumptions, and a brief description of the two samples utilised.

Chapter 3: Methodology and Samples

3.1. Overview

An outline of the research hypotheses examined in subsequent Chapters of this thesis was provided at the end of Chapter 2. Testing the majority of these hypotheses requires the use of quantitative genetic designs, and the current study has selected the twin design for this purpose. Although the fundamental concepts of the twin design have already been summarised (Section 2.2.2.2), this Chapter examines in greater detail the core assumptions upon which it is based and the key arguments used against its validity. How its principles are statistically implemented within a model-fitting framework for analytical purposes is discussed next. Of note, this Chapter presents only the basic twin model, and more complex analyses which build on this model are considered in subsequent chapters. The final purpose of this Chapter is to describe the two samples, one child and one adolescent and the measures collected in each, used to test the study hypotheses featured in subsequent Chapters.

3.2. Twin methodology

3.2.1. Key Concepts

Behavioural genetic designs belong to the category of methodological approaches which examine individual differences. Thus, they are premised on well-documented findings that almost all measurable phenotypes show variation around the population mean (Neale & Maes, 2001). These approaches are concerned with explaining the differences between individual members of a population and differ from group differences approaches, which compare mean levels of the expression of a phenotype between two or more groups in a population. Thus group differences analyses will focus on establishing differences between two groups (e.g. males and females) in the *level* of

depression symptoms, or in the increased rates of depression, which emerge from childhood to adolescence. However an individual differences approach examines the *causes* leading to differences between individual members of any group. It is important to emphasise that these two levels of analysis focus on somewhat different questions and may not necessarily be connected. Thus males and females, and children and adolescents may differ in the *mean* expression of the phenotype, but may be similarly affected by the *same* aetiological influences that cause individual differences.

Conventional individual differences approaches as applied by psychological, sociological and epidemiological studies typically account for variability in one set of measures (dependent variables or outcomes) by variation in a second set (independent variables or predictors) through regression methods (see Kline, 2004 for a review). What is unique to quantitative genetic designs is that variance in a phenotype is attributed to two causal but latent (unmeasured) influences: genes and the environment. Genetic influences are divided into additive (A) and dominant (D) effects, whereas environmental influences are either shared (C) or non-shared (E) (see Plomin et al, 2001 for a review). Additive genetic influences are those which show simple additive effects, such that two copies of a risk allele confers twice as much as risk as possessing only one copy. Thus the independent effects of alleles 'add up' to influence individual differences. In contrast, dominant genetic effects refer to interactions between alleles at the same or different genetic locus, such that the effect of one allele depends on that of another. Thus possessing two copies of the allele could result in more than twice the risk, or just one can confer no risks. Shared environmental influences are aspects of the environment resulting in increased similarity among family members (including twins and siblings) growing up in the same family, and non-shared environmental influences are individual-specific factors contributing to differences between family members. The goal of quantitative genetics is to partition phenotypic variance into these latent genetic

and environmental sources through quasi-experimental methods (Neale & Maes, 2001) and the twin design represents one paradigm through which these effects can be parameterised. An important assumption to note which applies to all quantitative genetic designs is that the estimates derived relate to a particular population of genotypes at a specific time in its historical context. As such, extraneous variables such as evolution or culture, which may change gene frequencies, the expression of genetic effects, or the frequencies of environmental events respectively, can impact upon the findings of quantitative genetic studies (Neale & Maes, 2001). Thus interpretations of the results of twin studies need to be made in the context of this potential caveat.

Notwithstanding this, the twin design represents a valuable tool for the estimation of genetic and environmental effects, which is premised upon relative differences in within-pair similarities between monozygotic (MZ) twins, dizygotic (DZ) twins and sometimes, full siblings (FS) on a phenotypic measure. Specifically the within-pair similarity, indexed through twin (or sibling) correlations, among each of these zygosity types may be a function of the degree to which twins (and siblings) share genetic and environmental factors. MZ twins originate from the same fertilised ovum and so they share all of their genetic material including both additive and dominant influences. However DZ twins and full siblings are created from different ovum, thus these individuals share on average half of their additive genes but only a quarter of dominant genes. In contrast both types of twins and all full siblings share their family environment to the same degree. Finally as non-shared environmental effects are by definition, individual-specific, not one of the pairs of related individuals share this aspect of the environment. As such based on these differential relationships, it is plausible to attribute increased MZ twin correlations compared to DZ twin (and/or full siblings) correlations on a phenotypic measure to their increased genetic similarity. Variance accounting for MZ twin similarity over and beyond genetic influence is

assigned as shared environmental effects. Lastly, non-shared environmental variance is inferred from any differences between MZ twins.

Such simple comparisons of twin and sibling correlations to yield genetic and environmental estimates form the theoretical basis of twin models. However scientific validation of these models necessarily involves estimating each term, testing for statistical significance and establishing how well the model explains observed data. Thus these simple calculations need to be implemented in a framework that allows for more sophisticated statistical analysis. Before describing the intricacies of this framework, which involve techniques borrowed from path analysis, matrix algebra and structural equation modelling, it is important to consider potential limitations that may compromise drawing definitive conclusions from twin studies.

3.2.2. Limitations of the twin design

Despite constituting the 'perfect natural experiment' (Galton, 1865) for which to explore the effects of genes and the environment on behavioural phenotypes, the twin study is not without its limitations and its findings must be considered in the context of several design-related caveats. Four issues, which have challenged the validity of findings from twin studies, have been raised. These are the accuracy of determining zygosity, the equal environments assumption and chorionicity, presence of assortative mating and the generalisability of findings.

3.2.2.1. Zygsosity classification

Given that the twin design relies on the comparison between pairs of MZ and DZ twins, it follows that accurate classification of these zygosity groups is essential. Any incorrect assignment can have important ramifications for the size of MZ relative to DZ twin correlations, upon which estimates of heritability are based. For example, misclassifying

MZ twins as DZ twins can artificially increase the within-pair similarity among DZ twins, simultaneously decreasing the difference between MZ and DZ twin correlations. This results in an attenuation of genetic effects but an increase in shared environmental effects. To minimise the effect of misclassification, zygosity testing can be conducted through the comparison of DNA markers in several highly polymorphic regions. If members of a twin pair differ on any DNA marker (excluding laboratory error) they are assigned as DZ twins. However if there are no differences at any of the markers, they are classified as MZ twins. Despite constituting the most accurate form of zygosity assignment, these procedures are costly both in terms of financial and time constraints, leading many larger studies to rely primarily on questionnaire-based measures.

Given that physical traits, such as eye and hair colour are highly heritable, and influenced by many different genes, the degree to which they are shared between members of a twin pair is a fairly reliable indicator of zygosity. As such these questionnaires utilise items relating to physical similarity between twins, the most common analogy being whether the children resemble 'two peas in a pod' to ascertain zygosity. Responses to these items generally lead to a bimodal distribution, with one sub-population representing identical (MZ) twins and the other non-identical (DZ) twins, upon which cut-off scores can be used to make the classification. In practice however, there are also pairs of individuals who fall in the middle of these distributions, reflecting ambiguous zygosities. Although accuracy rates as high as 95% have been reported (Goldsmith, 1991), which are unlikely to result in significant departures in estimates of heritability, there is still a sub-set of children at-risk for misclassification. Where possible, these may be followed up with genotyping, thus using a combination of questionnaire and molecular based methods to ensure accuracy (Chen et al., 1999).

3.2.2.2. Equal Environments Assumption

One of the key assumptions of the twin method is that of equal environments between MZ and DZ twins (Plomin et al, 2001). That is, environmentally caused similarity between both types of twins reared in the same family is equal. This can be violated if MZ twins are demonstrated to experience more similar environments than DZ twins, which result in either an overall increased phenotypic resemblance among MZ twins or raise the chances of exposure towards an environmental risk factor. In either scenario, the 'environmental concordance' among MZ twins is amplified relative to that between DZ twins, which can artificially inflate heritability estimates. MZ twins may experience more similar environments in at least two ways. Pre-natally, they may share more similar gestational environments to one another compared with DZ twins given that approximately two thirds of MZ twins develop in the same chorion, the sack within the placenta where the foetus develops, whereas all DZ twins develop in separate sacks. In their post-natal environments, MZ twins may also be perceived and treated more alike by others in comparison to DZ twins, due in part to their closer physical resemblance.

To ensure that such violations do not impact upon the findings of twin studies, it is critical to demonstrate that these documented differences in environmental exposure between MZ and DZ twins do not lead to environmentally-induced similarities among MZ twins for risks towards behavioural outcomes. Studies have generally found in favour of the equal environments assumption. First, MZ twins who are monochorionic (develop in the same sack) are no more alike in terms of their risk for psychopathology, compared to those who are dichorionic (develop in separate sacks) (Riese, 1999). Second aspects of increased post-natal environmental sharing among MZ twins, such as sharing a bedroom for a greater length of time during childhood do not predict subsequent similarity in the risk for depression (Cardno et al., 1999). Third in cases where parents have mistaken MZ twins as DZ twins or vice versa, such variations in

parental treatment have not influenced subsequent twin resemblance in depressive symptoms (Kendler, Neale, Kessler, Heath, & Eaves, 1994). A final argument suggests that the increased similarity in environmental exposure of MZ twins may be driven by genetic similarities mediated through behaviour rather than environmentally-induced. This suggestion is derived from findings that many aspects of the social environment, such as perceptions of parenting, life events and peer groups are genetically influenced (Plomin & Bergeman, 1991). If this were true, exposure towards more similar environments would fundamentally constitute a genetic effect, and thus its impact on overall heritability estimates would be correctly taken as such (Plomin et al, 2001).

3.2.2.3. Assortative Mating

A third source of scepticism regarding the validity of the twin study relates to the presence of assortative mating, or the tendency of individuals with similar phenotypes to mate more frequently than expected by chance. The presence of this phenomenon can alter genotypic frequencies, and thus genetic variance among families, which in turn may result in a corresponding increase in the proportion of predisposing genes shared between DZ twins, beyond the expected 50%. The effect of this is to inflate the resemblance among DZ twins, thus under-estimating genetic effects. Although assortative mating has been documented among affective disorders, it is typically reported more in bipolar disorder than major depression (Mathews & Reus, 2001), which is the phenotype examined in this thesis.

3.2.2.4. Generalisability of findings

The final question regarding the validity of twin designs is whether twins are representative of the general (non-twin) population. Twins may have atypical obstetric and perinatal histories, and suffer from birth complications and low birth weights more frequently than singletons (Phillips, 1993), and these differences may lead to variations

in behavioural, emotional and cognitive development among twins compared to singletons. However existing studies addressing this issue, indicate that with the exception of a slight initial delay in language development during the first three years of life (Rutter & Redshaw, 1991), twins are largely indistinguishable from non-twins in terms of behavioural and emotional problem behaviours (Moilanen et al., 1999). Furthermore, twins have been shown to report comparable levels of depressive symptoms to their singleton counterparts (Moilanen et al, 1999). These similarities have implications for whether findings from twin studies can be extrapolated to explaining individual differences in the general population.

In summary, the twin design is not without its flaws and these shortcomings should heed caution in regarding the estimates derived from these studies as absolutes. Where limitations have been raised, the twin design has generally proven to be remarkably robust in many of its assumptions. Perhaps its greatest strength lies not in providing indices of heritability, but rather as a springboard upon which the role of genes and the environment on behavioural phenotypes can be explored. This usage of the twin design as an exploratory tool has been greatly aided by application of mathematical modelling techniques to its core principles, a topic that will be considered next.

3.2.3. A statistical framework for the analysis of twin data

Having outlined the theoretical rationale of the twin design, the next step is to translate principles of this theory into a framework that allows for statistical analysis. Structural equation modelling (SEM), which draws upon the techniques of path analysis, matrix algebra and maximum likelihood estimation, mediates between the logic of theory and the reality of data (Neale & Maes, 2001). There are two aspects to structural equation modelling: building and fitting a model which will be discussed in turn.

3.2.3.1. Model Building

The first step in formulating a model is to translate the ideas of a theory into a mathematical format (Neale & Maes, 2001). The first assumption of quantitative genetic designs is that phenotypic variance (V_P) can be partitioned into genetic and environmental sources. Each of these can be further divided into additive (a^2) and dominant (d^2) genetic, and shared (c^2) and non-shared (e^2) environmental variance components. This decomposition can be summarised in a mathematical equation:

$$V_P = a^2 + d^2 + c^2 + e^2$$

The second assumption of the twin design is that MZ, DZ and FS correlations (r_{MZ}, r_{DZ}, r_{FS}) each reflect the different degrees to which these related individuals share genetic and environmental factors. Thus MZ twins share all their genetic material and shared environment; DZ twins and full sibling pairs share half their additive genetic effects, a quarter of dominant genetic effects, and all their shared environment. These differential proportions which account for the respective twin correlations can be re-expressed in mathematical formulae as:

$$r_{MZ} = a^2 + d^2 + c^2$$

$$r_{DZ/FS} = \tfrac{1}{2}a^2 + \tfrac{1}{4}d^2 + c^2$$

As there are only three observed statistics (phenotypic variance, MZ twin correlation and DZ twin correlation), from which to estimate the values of four unknown parameters, as featured in these equations (a^2, d^2, c^2, e^2), it is not theoretically possible to identify a unique estimate for each parameter (under-identification), thus one parameter must be excluded. Depending on the pattern of twin correlations, this is typically shared environmental (c^2) or dominant genetic (d^2) variance. Genetic dominance is normally inferred when DZ (or FS) correlations are less than half of those of MZ twins. If the correlations show otherwise, shared environmental effects are

estimated. As most of the models described in this thesis do not suggest genetic dominance effects, this latent factor is not described further in this Chapter. Without this component, the equations appear as simultaneous algebraic equations, whereby it is plausible to derive each term. Of note, as correlations are used to index twin similarity, phenotypic variance of the measure (V_P) is standardised to 1.

Equation 1 $$V_P = a^2 + c^2 + e^2 = 1$$

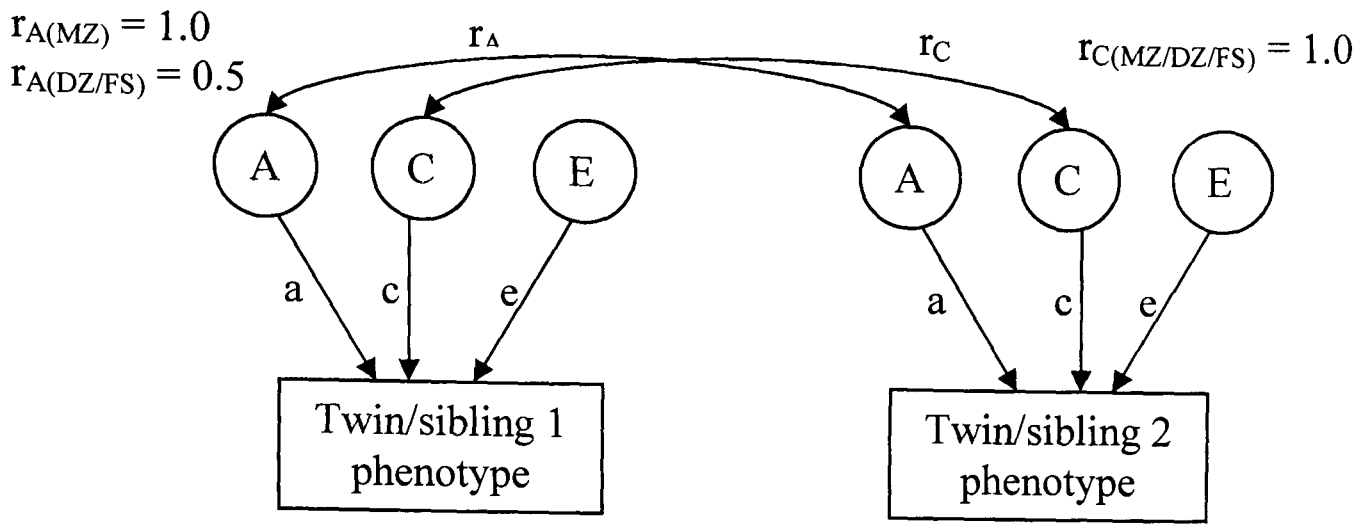
Equation 2 $$r_{MZ} = a^2 + c^2$$

Equation 3 $$r_{DZ/FS} = \tfrac{1}{2}a^2 + c^2$$

Accordingly, heritability assuming additive genetic effects can be estimated as twice the difference between MZ and DZ/FS correlations: $a^2 = 2(r_{MZ} - r_{DZ/FS})$. Shared environmental effects are the difference between MZ twin correlations and estimated heritability: $c^2 = r_{MZ} - a^2$. Finally, non-shared environmental effects constitute the remaining phenotypic variance: $e^2 = 1 - (a^2 + c^2)$ and as such also includes any measurement error that may be present. Whilst the comparison of twin correlations allows the rough estimates of heritability and environmental effects to be calculated, they cannot determine whether each of these terms is significantly different from zero. Furthermore as correlations have been standardised, they do not take into account variance within measures. As such a more common approach is to parameterise observed variance-covariance matrices using structural modelling techniques.

Structural equation models are often visualised using a graphical path diagram (Figure 3.1), which summarises the relationships between latent factors (A, C, E) and the observed variables (twin 1 variance, twin 2 variance and twin 1-twin 2 covariance). Latent (unmeasured) variables are typically depicted by circles or ellipses whereas observed (measured) variables are represented by rectangles or squares. Single headed arrows or 'paths coefficients' define causal relationships in the model, whilst double headed arrows indicate covariances or correlations (Hox & Bechger, 1998).

Figure 3.1: Univariate genetic analysis of twin and sibling data. A, C and E represent genetic, shared environmental and non-shared environmental factors respectively.



The information represented in the path diagram is equivalent to that presented in the algebraic equations described previously (equations 1-3). It is assumed that the variance in each twin is accounted for by the paths from the three latent factors (A, C, E). According to the rules of path analysis, to obtain the variance of a measured variable, each path coefficient is traced backwards along an arrow and then forwards (a * a'), resulting in their product (a^2). The total variance in each twin is obtained by the sum of the products from each of the three paths, equivalent to equation 1:

$$V_P = (a * a') + (c * c') + (e * e') = a^2 + c^2 + e^2$$

The covariance (or correlation) between the twins follows a different set of path tracing rules, and is derived by summing contributions from all paths by which the variables are connected. As seen in the path diagram, there are two connecting paths between twin 1 and twin 2 variables: through genetic relatedness (r_A) and through shared environmental relatedness (r_C), which index respectively the extent to which there are shared genes and shared environments between each member of a twin pair. Deriving the connecting paths between twin 1 variables to twin 2 variables necessarily involves multiplying the elementary paths, that is, the path coefficients of the causal arrows with the connecting path coefficient. This is done separately for the path involving genetic relatedness (a *

r_A * a') and for the path involving shared environmental relatedness (c * r_C * c'). Each contribution is then summed to yield the expected covariance (or correlation):

$$r_{(\text{twin 1})(\text{twin 2})} = (a * r_A * a') + (c * r_C * c')$$

As r_A and r_C have different values for MZ and DZ (or FS) pairs, the within-pair correlations will be different:

$$r_{MZ} = (a * 1 * a') + (c * 1 * c') = a^2 + c^2$$

$$r_{DZ/FS} = (a * \tfrac{1}{2} * a') + (c * 1 * c') = \tfrac{1}{2}a^2 + c^2$$

It can therefore be seen from this diagram, that the equations derived are identical to those described previously (equations 2 and 3).

In summary, a statistical model which estimates genetic, shared and non-shared environmental factors can be built using the set of equations derived from path analysis. Of note, the features of the basic twin model considered in this chapter can be extended to incorporate more complex effects that explore the nature of genetic effects in relation to sex differences (Chapter 4), developmental change (Chapter 4), differences within extreme groups (Chapter 4), moderation of genetic effects by measured environments (Chapter 5) and the analysis of two or more variables (Chapter 5, 6). In addition, the use of path analysis can also be used to build models which explore non-genetic effects, such as mediation and moderation amongst psychosocial variables and a phenotypic outcome (Chapter 7). The specific models, which include these more sophisticated features, are described in further detail in subsequent chapters.

3.2.3.2. Model-fitting

Having formulated a statistical model, these equations are then used to imply an expected structure for the variance-covariance matrices observed in the data. Maximising the agreement between this expected structure and the observed structure is the goal of model-fitting. A widely used method for estimation is Maximum Likelihood

(ML), which uses an iterative process to identify parameter estimates that best explain the observed data. An important assumption of ML estimation is that of multivariate normality, such that all measured variables and their covariance are normally distributed. An example of SEM software, using ML specifically for analysing the variance-covariance structures in twin data is Mx (Neale, Boker, Xie, & Maes, 1999). Mx evaluates matrix algebra expressions through the use of a simple language. Single letters represent matrices whilst certain characters and syntax are used to denote matrix operations and functions. As such structural equations and mathematical models can be easily specified. Data can be read into Mx in several formats including variance-covariance matrices and raw continuous data. Depending on how data is inputted, various statistics indexing goodness-of-fit and the number of degrees of freedom (df), typically required to determine the significance value (p) of the fit statistic, are provided. As raw data analysis is particularly appropriate for handling large datasets where missing data is common, all analyses in subsequent chapters are performed using a raw data approach. The fit functions appropriate for these data are described.

Comparing observed values against expected values produces a statistic called the log-likelihood. In raw data analysis, a function of this log-likelihood, twice the negative log-likelihood (-2LL) of the data is produced. The number of degrees of freedom is calculated by subtracting the number of estimated parameters from the total number of data points. Whilst -2LL does not represent an overall measure of model-fit, relative measures of fit, such as Chi-square (χ^2) can be obtained by subtracting the difference in the log-likelihood statistic of a tested model with that of a saturated model containing the same number of measured variables. A saturated model estimates the maximum number of parameters to describe variances, covariances and means of all measured variables from raw data. Variance-covariance matrices, which contain three estimated parameters (variance of each twin or sibling score and their covariance) for a measured

variable are modelled as a function of S * R * S', where S represents a matrix of standard deviations and R is a matrix of correlations. The means model estimates separate means for each individual of a twin or sibling pair. Thus a total of five parameters are estimated to describe these summary statistics. In saturated models, the total number of estimated parameters equals the total number of observed statistics provided, and is essentially a descriptive model that fits the data perfectly. As such it is used in the calculation of the χ^2 statistic with the difference in degrees of freedom between the tested model and the saturated model, used to determine the significance of this statistic. Although the primary use of saturated models is to obtain indices of model-fit, it is also used in descriptive analyses as detailed in Chapter 4.

In general, the lower the χ^2 relative to the degrees of freedom (i.e. a non-significant χ^2) indicates that the discrepancy between the expected and observed values is lower, thus the better the fit of the model to the data. However these fit statistics have the problem that their power varies with sample size, such that for a very large sample, the statistical test is almost certainly significant even when the model provides a good fit to the data. Conversely, with small samples, fit statistics may be adequate even though there is a bad fit. An alternative index of fit often used for large sample sizes is the Root Mean Squared Error Approximation (RMSEA), which is calculated as:

$$\left(\frac{\left\{ \frac{\chi^2 - df}{n} \right\}}{df} \right)^{\frac{1}{2}}$$

where ½ denotes the squared root of the value calculated within the whole bracket. By dividing by the number of participants with available data, as specified in the equation, the primary usage of this statistic is to provide an index of fit that takes into account sample size. Where estimates have been generated from the data of multiple groups, such as the use of within-pair covariance across different zygosity groups to derive

genetic and environmental parameters, RMSEA is multiplied by the square root of the total number of groups (Neale et al, 1999). Essentially RMSEA can be conceived as a weighted sum of discrepancies. Values falling below 0.10 indicate a model of good fit whereas values below 0.05 suggest a very good fit. In multivariate analysis, where different variables are likely to have different numbers of participants (due partly to missing data), the lowest 'n' was used in the calculation of this index, reflecting a more conservative approach. Of note, RMSEA cannot be calculated in instances where the degrees of freedom exceed the value of χ^2 as this leads to a negative result within the bracket, from which the square root cannot be taken. In this instance, the low χ^2 is sufficient in itself to demonstrate good fit.

A concurrent consideration of model-fitting in addition to obtaining parameters of best fit is to identify the model with the fewest parameters as possible, known as the principle of parsimony. Accordingly, the best-fitting model is the one with fewest parameters but which also possesses the lowest fit statistic. The Akaike's Information Criterion (AIC), which is calculated as $\chi^2 - 2df$ is an index of both goodness-of-fit and parsimony. A more negative AIC value indicates both good model fit and parsimony.

The most widely used application of the principle of parsimony lies in the comparison of alternative models, particularly when each offers a different account of the nature of genetic and environmental effects. As discussed earlier, different models are constructed using the rules of path analysis to derive a set of algebraic equations. These are then used to generate expected variance-covariance matrices which are subsequently compared with the observed structure in the data. Determination of the correct model occurs in the latter stages of model-fitting, where selection is based on the model with fewest parameters (parsimony) but the lowest χ^2 fit statistic. This application of model-

fitting to test competing explanations is exemplified in subsequent chapters that examine sex, environmental moderation and phenotypic causal paths.

Obtaining the most parsimonious solution is also often used to justify the dropping (or equating) of parameters to produce 'nested' sub-models. In these comparisons, the choice of a sub-model over the full model is based on whether excluding (or equating) certain parameters results in a significant worsening in fit relative to the change in degrees of freedom (Δdf). Change in fit is indexed through a comparison of the -2LL statistic of each (raw data) model, which yields a χ^2 statistic. However if the χ^2 statistics have already been derived for each model (through comparison with a saturated model), the difference between these χ^2 statistics can also indicate changes in fit. In either scenario, a significant χ^2 represents a significant departure of the model from the observed values, and indicates the importance of the excluded parameter (or that parameters cannot be equated). A non-significant change in χ^2 has been used as evidence for the absence of effects associated with an excluded parameter (or that parameters can be equated). However excluding parameters on the basis of a lack of change in fit has been criticised (Rutter, Silberg, O'Connor, & Simonoff, 1999) given that this may also be related to a lack of power to detect effects rather than an absence of such effects. A better indication of the presence and significance of parameter estimates is to present confidence intervals of all parameters in the full model.

3.3. Twin Samples

The majority of study hypotheses in this thesis explore the nature of genetic and environmental effects on depression in two different aged samples. An outline of the selection process, timeframe of data collection, participant characteristics and measures collected from each sample are presented in this section. Given that more analyses are conducted using the adolescent sample, this is described first.

3.3.1. G1219: An adolescent twin and sibling sample

3.3.1.1. Selection process

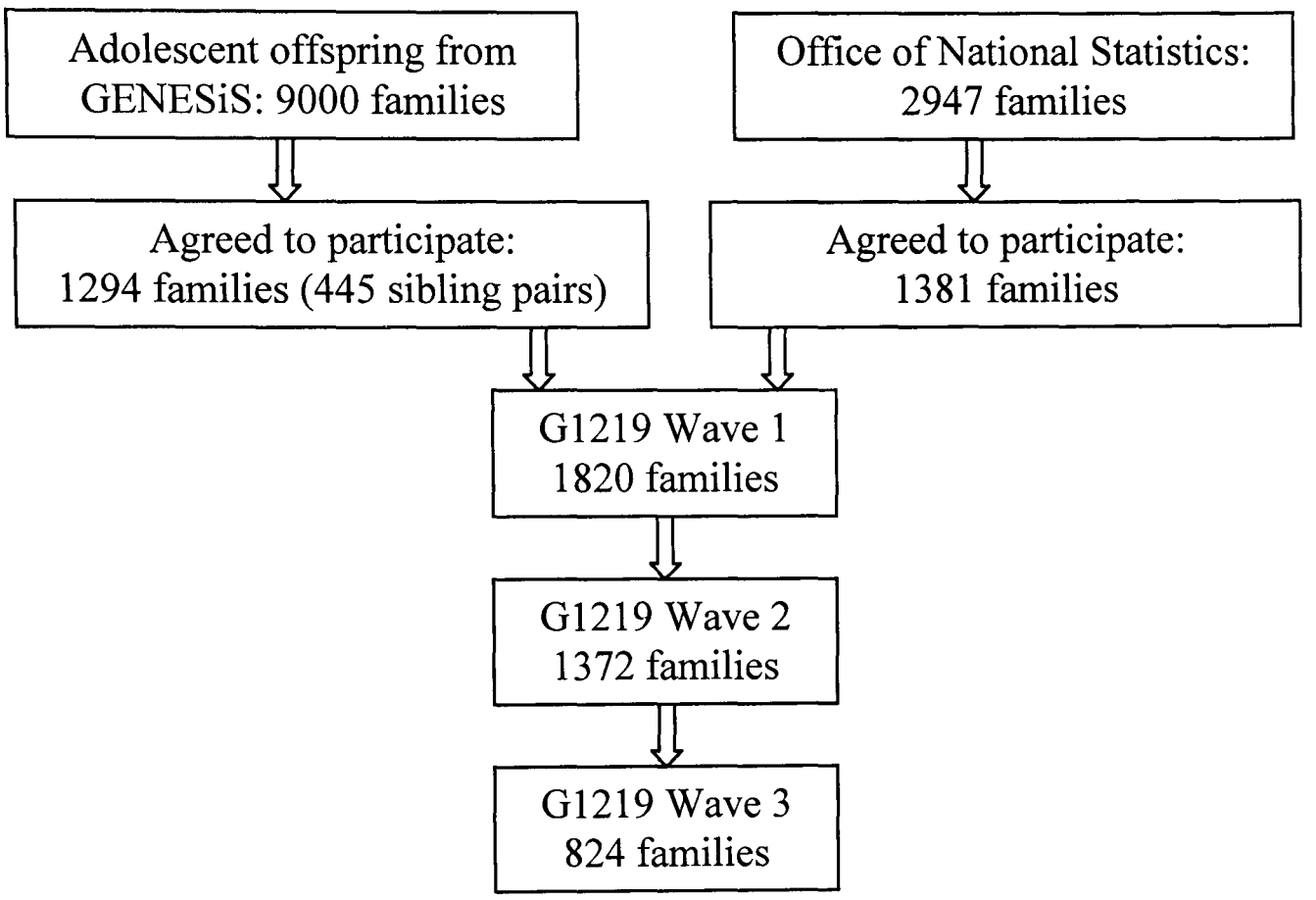
The G1219 study is a longitudinal study of 3640 adolescent twins and siblings aged between 12 to 19 years at initial contact. Questionnaires were sent to adolescents and their parents at three time-points over a period of approximately 2 years 8 months (range 1-5 years). Informed consent was obtained from parents of all adolescents under 16, and from the adolescents themselves when over 16. Ethical approval for this study was given by the Research Ethics Committee of the Institute of Psychiatry and South London and Maudsley NHS Trust.

Initial recruitment of the sample was from two different sources. In the first, the adolescent offspring of 9,000 adults participating in a large-scale population-based study (GENESiS: Genetic-Environment Study of Emotional States in Siblings, Sham et al., 2000) were contacted and invited to participate in this study or another study of hyperactivity (Curran et al., 2003). Of the 3,600 responses received, a total of 1,818 (20%) adolescents from 1,294 families agreed to G1219, of which 445 were full sibling pairs. The second source of recruitment was from a random selection of live twin births born between 1985 and 1988 identified by the UK Office of National Statistics. Health Authorities and General Practitioners contacted 2,947 families of whom 1,381 (47%) agreed to participate. Only respondents aged 12- to 19-years were retained in the study. As the current analyses focus on twin and sibling data, this left 1,820 families.

Contact invitations included questionnaires to adolescents and their parents (Wave 1). A second set of questionnaires was sent to adolescents only and were returned approximately 8 months after initial contact (range: 0-2 years) by 2,651 individuals (73%) from 1,372 families (Wave 2). A third set of questionnaires, approximately 25 months (range: 1-4 years) after Wave 2 data collection were sent to both adolescents

and parents. These were returned by 1,597 adolescents (43%) from 824 families, and 836 parents (46%). A summary of the selection process and the response rates of the study at each Wave is presented in Figure 3.2.

Figure 3.2: Selection process including initial recruitment and response rates at each wave of data collection for the G1219 sample



3.3.1.2. Participant characteristics

Zygosity was established through a questionnaire measure completed by parents at waves 2 and 3, assessing physical similarity between twins (Cohen, Dibble, Grawe, & Pollin, 1975). When zygosity was only available on one wave, this rating was used. If there were disagreements between zygosity rating at two waves, DNA was obtained (N = 26 pairs). Final classifications are currently being made. At the time of writing this thesis, the entire G1219 sample consists of 168 MZ male twin pairs, 199 MZ female twin pairs, 138 DZ male twin pairs, 190 DZ female pairs, 463 opposite-sex DZ pairs, 109 male sibling pairs, 132 female sibling pairs and 186 opposite-sex sibling pairs. This left a total 235 pairs of unknown twin zygosity, including the 26 pairs with conflicting

zygosity ratings across waves. 51.7% of the initial sample was female and 47.4% was male. At waves 2 and 3, the proportion of females to males was 56.1% to 43.9% and 58.7% to 41.3% respectively. The mean age of the sample at waves 1, 2 and 3 were 14 years 5 months (range 12-19), 15 years (range 12-21) and 17 years (range 14-23).

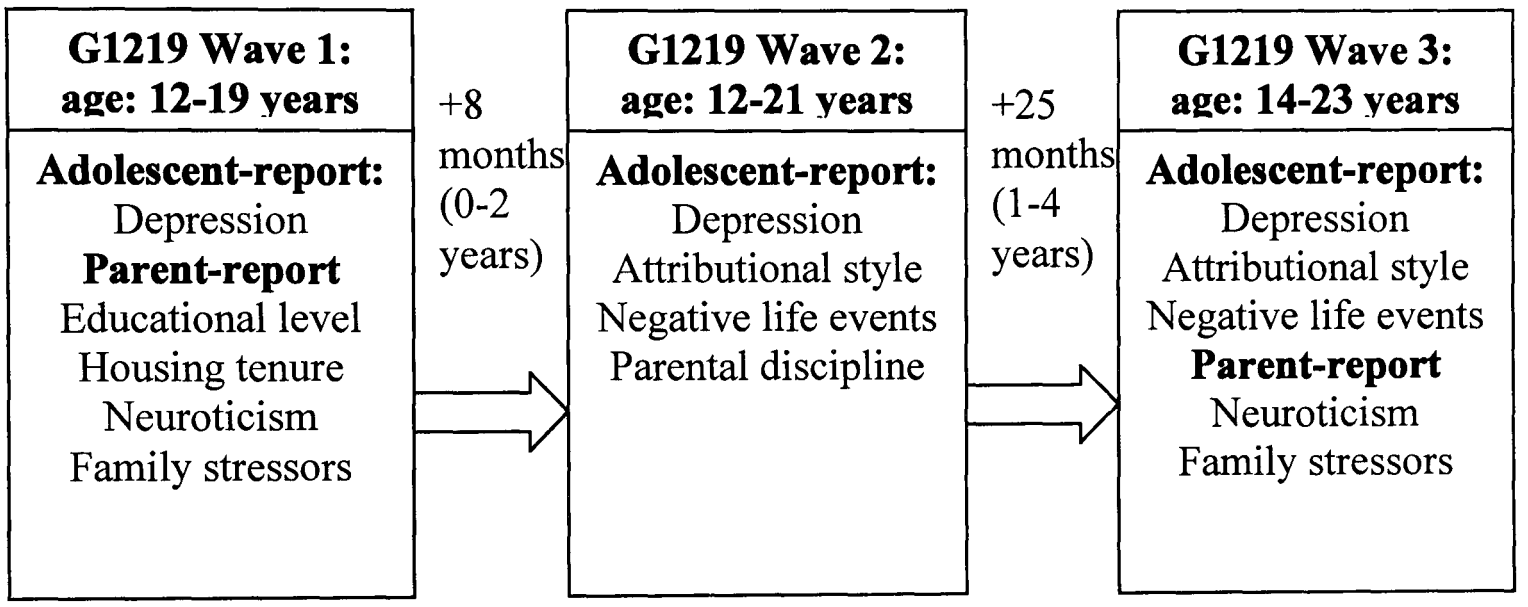
Levels of parental education were somewhat higher (39% educated to A-level or above) than in a large nationally represented sample of parents (Meltzer, Gatward, Goodman, & Ford, 2000) where 32% were educated to A-level or above. G1219 parents were also somewhat more likely to own their own houses (82%) than in the nationally representative sample (68%). To reduce the impact of any initial response bias associated with educational level, the sample was re-weighted to match the distribution of educational qualifications in a nationally representative sample of parents (Meltzer et al, 2000). This weight was used in all analyses, which only examined Wave 1 data. To account for any attrition between Waves 1 and 2, a second weight was created, by assigning scores based on Wave 1 predictors of non-response at Wave 2. Predictors included sex of the child (response more likely from girls), housing tenure (response more likely from owner-occupiers), and educational levels of parents (response more likely from individuals with parents reporting higher qualifications). These scores were then multiplied with the Wave 1 weight to incorporate initial response bias. This weight was used for analysing Wave 2 data only or joint analyses of Wave 1 and 2 data. A third weight was generated to account for further attrition by Wave 3. As before, sex of the child, housing tenure and the educational level of parents continued to predict wave 3 responses. Additionally, self-reported adolescent delinquent behaviour was also a significant predictor. Scores were assigned according to these predictors, and multiplied by the Wave 2 weight, thus simultaneously taking into account the initial response bias and attrition between the first two waves. This final weight was used in all analyses which involved Wave 3 measures. Of note, all weights were created to be family-

general, such that in model-fitting analyses, the weights did not incur any additional individual-specific effects between members of the same family.

3.3.1.3. Measures

Data collected at Waves 1, 2 and 3 were used in this thesis. A summary of the specific measures used, the time-frame at which they were collected and whether they were child- or parent-reports is presented in Figure 3.3. Each measure is discussed in the order in which it appears in the diagram. Items of all measures are listed in Appendix A.

Figure 3.3: Measures from three waves of data collection of the G1219 sample



Adolescent-reported depression symptoms: The Short Mood and Feelings Questionnaire (SMFQ: Angold et al, 1995) is a self-report questionnaire consisting of 13 items used to assess core depressive symptoms occurring over the past two weeks. As one of the initial aims of the G1219 study was molecular genetic analyses of extreme scoring groups (Eley et al., 2004), a four-point response format (never, sometimes, often, always) was used at the first two waves of data collection to allow better discrimination of the lower end of the spectrum. As such a different scale was used at Waves 1 and 2 to that in Wave 3. A total depression score was created by summing these responses. The SMFQ has good internal consistency (Cronbach's alpha = 0.90) and adequate test-retest reliability (0.66 for child-reports and 0.88 for parent-reports) (Costello & Angold, 1988;

Costello, Benjamin, Angold, & Silver, 1991). It also correlates well with other well-known measures of depression (0.67 with the Children's Depression Inventory and 0.51 with the depression scores from the Diagnostic Interview Schedule for Children) (Angold et al, 1995). There are also reports of reasonable sensitivity (0.60–0.75) and specificity (0.61-0.74) in discriminating between depressed and non-depressed cases (Thapar & McGuffin, 1998), although distinction between depression and other psychiatric diagnoses is considerably weaker. The internal consistency statistics, indexed by Cronbach's alpha are: 0.88, 0.90 and 0.88 for Waves 1, 2 and 3 respectively.

Parent-reported educational level: Parents selected their highest educational qualification from a list, which included the following categories: no qualifications, GCSE, CSE, A-level, HNC, HND, Degree, Postgraduate and Other. A text box was also provided for alternative or additional responses. Textual responses included vocational skills or job-related qualifications, and were subsequently rated by three independent researchers to one of the 8 categories or assigned as a missing score, if there was ambiguity. Disagreements between raters were resolved through discussion.

Parent-reported housing tenure: Parents were asked to indicate current housing tenure from one of 5 categories: Owned, Rented, Housing Association / Council, Living in parent's home or other.

Parent-reported neuroticism: The short form of the neuroticism scale from the revised Eysenck Personality Questionnaire (EPQ-N: Eysenck, Eysenck, & Barrett, 1985) was completed by parents. This consists of 12 items, which have satisfactory internal consistency and high test-retest reliability over a 4 week period (Alexopoulos & Kalaitzidis, 2004). Good concurrent validity with other well-known personality questionnaires has been reported (Aluja, García, & García, 2002). Furthermore, the factor structure of this questionnaire, upon which the neuroticism scale is derived, has

been replicated (Alexopoulos et al., 2004). Data from the current sample of parents yields a Cronbach's alpha of 0.80 and 0.81 at Waves 1 and 3 respectively.

Parent-reported family stressors: Two measures were used to generate an index of family-general stress, including the short version of the Social Problems Questionnaire (SPQ: Corney, 1988) and the List of Threatening Experiences (LTE: Brugha, Bebbington, Tennant, & Hurry, 1985). The first of these assesses social adversity through the presence and severity of difficulties in several aspects of the parent's life, including financial, housing, work, relationships and social activities. Parents are asked to rate these on a 4-point scale ranging from none to severe, and responses to each domain are summed to give an overall score of social adversity. Psychometric properties of this measure have been reported (Corney & Clare, 1985). Across the study sample, which included GP attenders, epileptic patients and social work referrals, specificity ratings (i.e. determining if a problem was absent given that it truly was absent) were generally higher across domains of the questionnaire than sensitivity ratings (i.e. determining if a problem was present given that it truly was present). Thus although the measure yields lower false negatives, there may be a tendency to under-estimate specific social problems. However in general, inter-rater agreement between patients and their spouses, and between social work referrals and their social workers on the presence/absence of problems was acceptable. The List of Threatening Experiences is a list of 12 negative life events, to which parents were asked to select those which had occurred in the past 6 months. This scale has been found to have high test-retest reliability with good agreement with information provided from other informants. Furthermore, high specificity and sensitivity were reported in comparison to social adversity rated using other well-known life event scales (Brugha & Cragg, 1990). Given the overlapping items between the SPQ and the LTE, scores on these measures were aggregated to create a composite reflecting familial social risk. As the items of these

questionnaires are presumed to be unrelated, indices of internal consistency were not reported.

Adolescent-reported Attributional style:

The revised Children's Attributional Style Questionnaire (CASQ: Kaslow & Nolen-Hoeksema, 1991) contains 24 forced-choice items that assess the three dimensions of attributional style (internal-external, global-specific and stable-unstable). Each item describes a positive or negative event (e.g. "You get an A on a test") followed by two possible causes of the event (e.g. "I am clever" or "I am good in the subject the test was in"), from which the individual must chose. Each set of response-options holds constant two of the three dimensions of attributional style, whilst varying the third, allowing for independent assessment of that dimension. A composite score is computed by summing all responses. Lower composite scores indicate more negative attributional styles. Exploration of psychometric properties (Thompson, Kaslow, Weiss, & Nolen-Hoeksema, 1998) show moderate internal consistency reliabilities are reported for the composite, ranging from 0.4 to 0.6. Test-retest reliabilities over a six month period have also been modest, at 0.53. Finally criterion-related validity assessed through associations with measures of depression are adequate ($r = -0.40$). Internal consistency of this measure was moderate in the current sample, as indexed by Cronbach's alpha (0.61 and 0.66 at Waves 2 and 3 respectively).

Adolescent-reported life events: The Life Event Scale for Adolescents (LES-A: Coddington, 1984) is a checklist of 50 events, whose occurrences are judged to require some degree of social readjustment by the individual. Of these, 24 are classed as negative and summed to create a total negative event scale. These events include those that arise 'independent' of an individual's behaviour (e.g. death of a parent) and those which are 'dependent' to some degree on an individual's actions (e.g. breaking up with

boy/girlfriend). Psychometric testing shows adequate test-retest reliabilities at 0.69 and 0.67 for a 3- and 7-month interval (Coddington, 1984). As with the List of Threatening Experiences and the Social Problems questionnaires, items of this questionnaire were also presumed unrelated, and indices of internal consistency unreported.

Adolescent-reported maternal discipline: The Negative Sanctions and Communication About Discipline sub-scales are adapted from a well-known measure of child-parent relationships (Hetherington & Clingempeel, 1992). These assess the use of punitive discipline (e.g. yell at you about what you did) and of constructive discipline including compromise and/or discussion (e.g. talk to you about what you did). Cronbach's alpha for these sub-scales have been calculated at 0.66 and 0.68 for Negative Sanctions and Communication About Discipline respectively (O'Connor, Dunn, Jenkins, Pickering, & Rasbash, 2001). In addition these sub-scales correlate well with other related questionnaire measures. Only data relating to maternal parenting behaviours were used in the current analyses. Internal consistencies for these scales were 0.80 for both as indexed by Cronbach's alpha.

3.3.2. TEDS-ECHO: A child twin sample

3.3.2.1. Selection process

The ECHO (Emotions, Cognitions, Heredity, Outcome) study is a longitudinal study of 600 twins aged 8 (range: 8 years 2 months to 8 years 11 months) at Wave 1 and 10 at Wave 2 (currently ongoing). The sample is a spin-off study from an ongoing longitudinal study (TEDS: Twins Early Development Study, Trouton, Spinath, & Plomin, 2002) of the early development of twins born in England and Wales during 1994-1996. Both waves of data collection took place at the Institute of Psychiatry with an interval of approximately 2 years between visits. Informed consent was obtained from parents of all twins. Ethical approval for this study was given by the Research

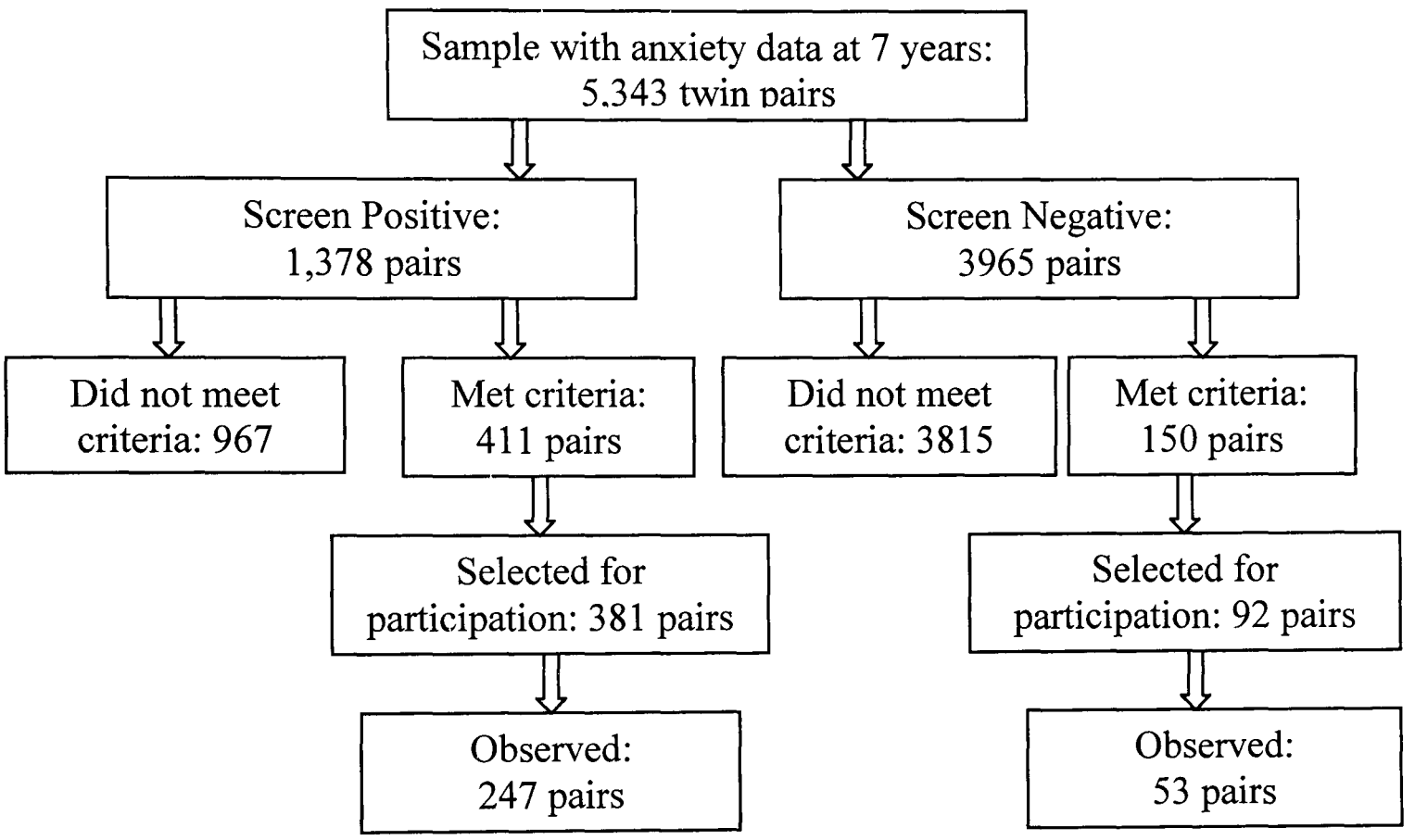
Ethics Committee of the Institute of Psychiatry and South London and Maudsley NHS Trust.

Selection for the ECHO study was based primarily on parental report of child anxiety at age 7. A summary of the selection process is presented in Figure 3.4. Of the 5745 families in TEDS, parental data was available for 5343 twin-pairs. 1378 of these families contained at least one child scoring in the top 15% of this scale (proband pairs). The number of pairs excluded (N = 967 in total) were as follows: withdrawn from TEDS (n=5 pairs), major medical condition such as spina bifida, cerebral palsy and autism (n=75 pairs), participating in other concurrent studies (n=211 pairs) and not living within a two-hour travel radius of the Institute of Psychiatry (n=676 pairs), leaving 411 potential proband families. A further 30 had moved. This left 381 proband families who were invited to participate, of whom 247 pairs agreed (65%). For the controls (N=3,965), the same criteria applied, excluding 2,794 pairs as follows: withdrawn from TEDS (n=25 pairs), major medical condition such as spina bifida, cerebral palsy and autism (n=102 pairs), participating in other concurrent spin-off studies (n=737 pairs), and not living within a two-hour travel radius of the Institute of Psychiatry (n=1,930 pairs), leaving 1,171 potential control families. From these a random 92 pairs were invited to participate, of whom 53 agreed (58%).

The total number of families seen at Wave 1 was therefore 300. Following assessment, data from 11 twin pairs (4%) were considered unusable because at least one of the twins had neurological impairments, autistic spectrum disorders, severe receptive language impairments or persistent difficulties with attention. Wave 2 data collection is currently ongoing. At the time of writing this thesis, 240 families had been contacted, 17 of these opted out of the study and an additional 6 were unreachable, leaving 217 who were subsequently tested (75% of the original sample excluding the 11 families whose data at Wave 1 was unusable). Most analyses in subsequent Chapters focus on measures

collected at Wave 1. A small proportion of analyses described in Chapter 4 also utilise data from the 186 families seen to date at Wave 2. Several parent-reported measures, collected as part of the TEDS annual assessment when the twins were 7 years, were also available for use in analyses featured in Chapter 7.

Figure 3.4: Selection process including initial screen, inclusion criteria and final response rates for the ECHO sample



3.3.2.2. Participant characteristics

A parent-rated zygosity questionnaire unambiguously identified 95% of the twin pairs as monozygotic or dizygotic. For the remaining 5%, DNA was collected from cheek swabs and zygosity was assigned using highly polymorphic markers that yield an accuracy of 99.9% (Price et al., 2000). The final sample used in these analyses consisted of 96 MZ and 192 DZ twin pairs and one pair of unknown zygosity and who refused participation in a DNA test. 57% of the sample was female and 43% was male. The majority of the families participating in the ECHO study are white (n=256, 87%). Most mothers are employed (n = 215, 74%) and remained in education until 18 years or later

(n = 157, 54%). Similarly, most fathers are employed (n = 269, 93%) and remained in education until 18 or higher (n = 175, 61%). Of the 186 families seen at Wave 2, 65 were MZ pairs and 121 were DZ pairs. 222 were female and 150 were male. Twins were aged between 9 years 8 months and 10 years 11 months.

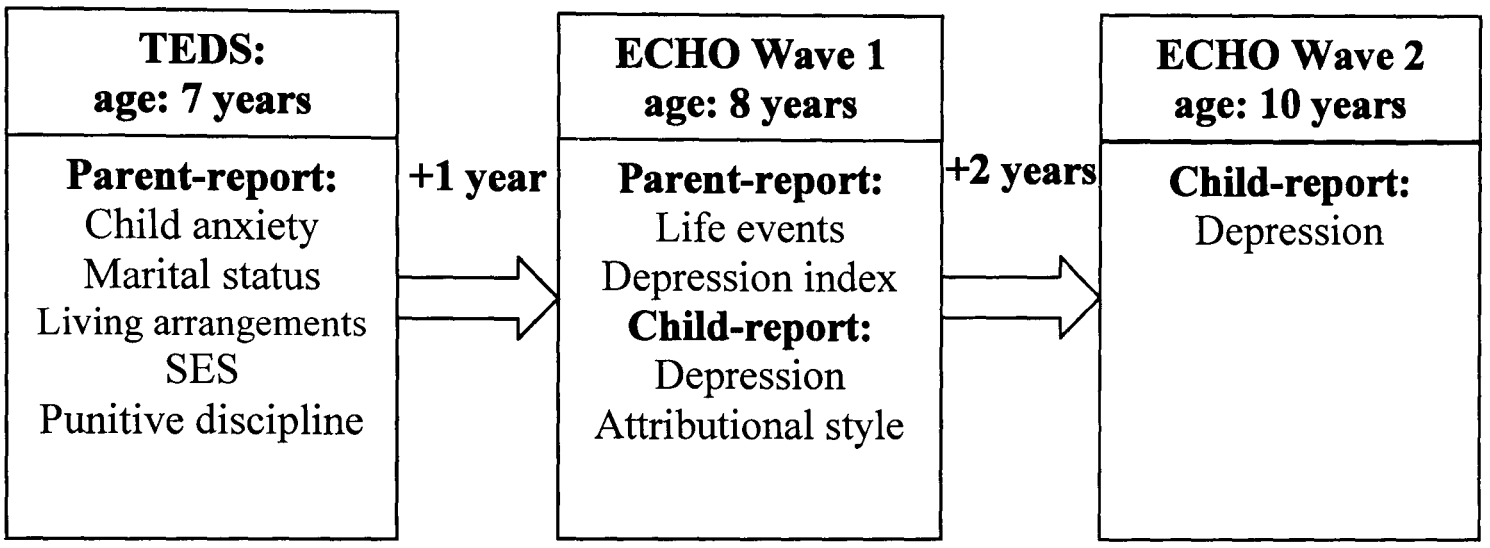
The TEDS study composite measure of SES (qualifications and current employment for both mother and father, and mother's age at the birth of her first child) was used to compare families that did and did not take part, finding that the former were of slightly higher SES than the latter (see Eley et al, 2005 for more details). There were also slight differences on the basis of the sex-by-zygosity group with MZ pairs both male and female more likely to participate (14.1% and 12.3% opted in and out of the study respectively for MZM and 19.0% and 13.0% opted in and out for MZF respectively), and DZ male pairs less likely to take part (10.0% and 15.4% opted in and out respectively, $\chi^2 = 14.20$, df = 5, $p < .05$). However, there were no differences in anxiety scores of the children (mean =13.55 and 13.36 for opted in and opted out respectively, p = ns) or ethnicity (13.4% vs 9.6% opted in and out respectively, p = ns).

Participants of the ECHO sample were selected from a larger study of twin pairs. Pairs where one twin scored in the top 15% of an anxiety scale and a random selection of control pairs, where neither twin scored in the top 15% of this scale were invited to take part. This method of recruitment can lead to increased means, decreased variances, and decreased covariance of correlated variables (Felsenfeld et al., 2000). To correct for the ascertainment bias, all ECHO variables were analysed jointly with the 7 year anxiety selection variable from the TEDS sample. This technique treats TEDS participants not included in the ECHO sample as "missing" in the testing phase. Any additional "missingness" is assumed to be due to random processes not related to the scales included in the ECHO study (see Little & Rubin, 1987).

3.3.2.3. Measures

Data collected in the main TEDS study at age 7, and at Wave 1 and 2 of the ECHO sample were used in this thesis. A summary of the specific measures used, the time-frame at which they were collected and whether they were child- or parent-reports is presented in Figure 3.5. Each measure is discussed in the order which it appears in the diagram. Items of all measures are listed in Appendix A.

Figure 3.5: Measures from three waves of data collection: TEDS age 7 assessments and Waves 1 and 2 of the ECHO sample



Parent-reported child Anxiety: A parent-reported composite of child anxiety was created using 5 items from the Strength and Difficulties Questionnaire anxiety sub-scale (SDQ: Goodman, 1997) and 16 items assessing symptoms of general anxiety, phobias, separation anxiety, anxious cognitions and shyness. Summing these together generated a scale with acceptable internal consistency (Cronbach's alpha = 0.81). This composite was used for initial selection of high-scoring anxiety individuals and controls into the ECHO sample. This variable was included in all analyses to correct for ascertainment.

Parent-reported marital status and living arrangements: Information on marital status and living arrangements as reported by parents were combined to create a categorical variable reflecting the current family composition (living with both natural parents, living with a step-parent and a one-parent household). Of the 300 families in ECHO,

this yielded frequencies of 258, 3 and 33 respectively, and 6 families with missing data. Given lower numbers associated with 'living with a step-parent' and 'one-parent household', these were aggregated to form a dichotomous variable indexing whether twins lived with both biological parents or not.

Parent-reported SES: Socio-economic status of families was computed from aggregating the standardised versions of five different variables. These indexed respectively fathers' highest education qualification, fathers' occupational status, mothers' highest qualification, mothers' occupational status, and age of mother at birth of eldest child (Pike, Iervolino, Eley, Price & Plomin, in press). A higher score on this variable reflects a higher socioeconomic status.

Parent-reported punitive discipline: Parental punitive discipline for each twin was measured using 6 questionnaire items derived from a semi-structured interview (Deater-Deckard, Dodge, Bates, & Pettit, 1998) in which parents were questioned on their use of discipline strategies such as hitting, shouting and being firm and calm. These items were rated on a 6-point scale from 'I rarely or never do this', to 'I usually do this'. After answering for the first-born twin, parents were asked "Do you do this more or less with your second-born twin?" and their answers rated on a 5-point scale from 'a lot more' to 'a lot less'. Thus whilst the first-born twins' scores were based on the sum of the Discipline items, which were standardised to zero mean and unit variance for the whole sample, scores for second-born twins were derived from comparisons with their co-twins, rather than from their own raw scores. To make first and second born twins' scores more comparable, each second born twin's score was recalculated as the sum of first twins' score and the standardised sum of the differential items about Twin 2 (i.e. I feel this way 'a lot more', 'a little more', 'about the same', 'a lot less' or 'a little less'). Internal consistency statistics were 0.50 and 0.77 for Twin 1 and Twin 2 scales.

Parent-reported Depression Index: Parental history of depressive episodes was indexed by the total number of positive responses parents gave to five screening questions. These enquired whether parents had experienced problems with nerves; referral to a psychiatrist; difficulties with nerves, tension or depression; consultation with professional regarding emotional problems; and/or multiple 'spells' of depression, anxiety or nerves (McGuffin, Katz, & Aldrich, 1986).

Parent-reported Life events checklist: A checklist of 11 events were selected from the Life Event Scale for Children (LES-C: Coddington, 1984) to index life events which had occurred in the last six months for each twin. The original LES-C consists of 36 events, including positive and negative, familial and personal items, and was developed as a parallel measure to its adolescent counterpart (LES-A). As each event is weighted according to its estimated stressfulness and time needed for readjustment, only events with a weight of above 50 were selected in the current checklist. As these were all negative events, the positive event with the highest weighting was also included making a total of eleven events. The ten negative events were aggregated to create a total negative events scale, and used in subsequent analyses. Most psychometric properties of this scale have been performed for the entire scale of the LES-C (Coddington, 1984) or the LES-A, the adolescent version, and are reported in the previous section. In addition, reasonable content validity of the LEC-S was established by showing that in 84.4% of administrations of the checklist to parents, no 'other' events were added. In general there is low agreement between child and parent reports of life events (r=0.27) with children reporting on average fewer events. However given that most items included in the current scale were more objective events, and of a more severe nature (for example, death of a sibling), it is likely that parents are accurate in their reports. Combined parent- and child-reported scores on the LED-C also showed good predictive validity in

the development of serious behaviour problems within one year. As with other life events measures, internal consistency statistics were not reported for these items.

Child-reported depression symptoms: Self-reported depression symptoms were assessed using the Children's Depression Inventory (CDI: Kovacs, 1981). This questionnaire consists of 27 items quantifying a range of depressive symptoms, including disturbances in mood, hedonic capacity, vegetative functions, self-evaluation and interpersonal behaviours. It was designed specifically to be comprehensible to school-aged children. Each symptom is evaluated through a choice between three statements (scored 0, 1, 2), which vary in severity or the frequency to which it is present. Total scores range from 0-54 however the version used in ECHO did not include a question assessing suicidal behaviours, making 26 items with total scores falling between 0-51. Psychometric properties of the CDI have been described in detail (Kovacs, 1985). Cronbach's alpha reliability indices show good internal consistency: 0.86 and 0.82 in a psychiatric sample of outpatient children and a diabetic control group. One-month test-retest data showed reasonable stability (r=0.82). Strong correlations with measures of anxiety and low self-esteem (r=0.65 and -0.59) and discrimination between different diagnostic groups, e.g. major depression and conduct disorder have been reported. It differentiates less well between high-scoring 'normal' children and psychiatrically depressed children, suggesting that it is more appropriate for rating severity rather than diagnoses. As such it is often used in the assessment of depressive symptoms in community samples. The current sample yields comparable internal consistency statistics (Cronbach's alpha = 0.82 and 0.81 for Waves 1 and 2 respectively).

Child-reported attributional style: The revised Children's Attributional Style Questionnaire (CASQ: Kaslow & Nolan-Hoeksema, 1991) described previously was also used in the child sample to assess attributional style. A modest internal consistency is reported in the current sample (cronbach's alpha = 0.55).

Chapter 4: Genetic and Environmental Influences on Child and Adolescent Depression Symptoms

4.1. Overview

Genetic explanations of vulnerability to depressive conditions in children and adolescents were considered in Chapter 2. Although these have been applied to understanding epidemiological trends in the presentation of depression, unresolved issues in relation to age and sex effects on genetic and environmental indices, the role of genetic and environmental factors on phenotypic continuity and change, and aetiological differences between normal ranged symptoms and those falling at the extreme end of the spectrum, remain. This Chapter aims to explore these existing issues in the child and adolescent samples described in Chapter 3. Three sets of model-fitting analyses, which build upon and adapt the basic twin model detailed in Chapter 3, were conducted. First main effects of age and sex on genetic and environmental indices were addressed. Second, the contribution of 'new' and 'stable' genetic and environmental influences to developmental continuity of the phenotype were examined. Third the aetiological influences on extreme scores were investigated. Clarifying these effects provides a greater understanding of the role of genetic risks, relative to the environment in creating vulnerability. Furthermore comparing the results obtained in childhood and adolescence allows insight into the developmental trajectory by which genetic and environmental risks are expressed. Findings were generally consistent with the existing literature. Cross-sectional comparisons of results obtained in the child and adolescent samples revealed a trend of increasing genetic but decreasing shared environmental effects across these developmental stages. Furthermore although genetic effects during adolescence contributed towards phenotypic continuity, 'new' genetic effects emerging around mid-adolescence were also found. In contrast, 'stable' and 'new' shared

environmental effects were involved in developmental continuity and change during childhood. Finally, a pattern of increased shared environmental effects, but reduced genetic influence characterised extreme-scoring individuals in both childhood and adolescence. No main effects of sex were found on genetic and environmental indices or in any of the developmental trends. Extreme-scoring females showed greater shared environmental effects compared to males at one time-point in the adolescent sample.

4.2. Background

The bulk of evidence from family and twin studies suggests that early-onset depression symptoms are both familial and heritable, with some contribution from shared environmental factors (Rice et al, 2002). However more detailed examination of these studies shows that the role of genetics in accounting for vulnerability to depression is not straightforward and instead its effects may vary with age and development, sex, and in individuals with more severe forms of the phenotype. Understanding the complex patterns of genetic and environmental effects on depressive symptoms is important as they may clarify several epidemiological trends in the presentation of depression. Most notably, genetic explanations have been applied to explaining the sudden rise in the rates of depression during mid-puberty, between the ages of 13 and 15 (e.g. Rice et al, 2003), and the increased preponderance among females in this age range. Second, they have contributed towards resolving the conflicting views of categorical and dimensional conceptualisations of depression (Deater-Deckard et al, 1997). Specifically changes in the size of genetic and environmental factors or in the emergence of 'new' influences may provide possible accounts of observed age- and sex-related trends on prevalence rates (e.g. Scourfield et al, 2003). Comparing genetic and environmental factors in high scoring individuals (those presumably at increased risk for disorder) with those falling

in the normal range can offer insight into whether the former set of individuals represent an aetiological disjunction, thus challenging (or validating) the proposed continuum.

However results from behavioural genetic studies have not been definitive. Of the existing literature, there are indications of increased genetic effects in adolescence compared to middle and late childhood (7-12 years) (Thapar & McGuffin, 1994; Hewitt et al, 1992; Eley & Stevenson, 1999; Silberg et al, 1999; Silberg et al, 2001; Rice et al, 2002; Scourfield et al, 2003). In contrast, shared environmental influences may predominate during middle childhood. Sex effects have characterised some samples (e.g. Hewitt et al, 1992; Eley & Stevenson, 1999; Silberg et al, 1999; Silberg et al, 2001) but not others (Bartels et al, 2003a, 2003b; Thapar & McGuffin, 1994; Gjone & Stevenson, 1997). Of those who have described positive findings, there is little consensus as to whether greater genetic effects are characteristic of males or females, or if these differences depend on the age of the sample. Studies using longitudinal data to examine if the same genetic and environmental factors contribute towards continuity in depressive symptoms across time or if newer aetiological influences become operational at a later time-point have provided an additional window into age-related changes. Whilst genetic factors may contribute towards continuity in symptoms in some developmental periods (e.g. adolescence) (O'Connor et al, 1998; Silberg et al, 1999), 'new' genetic effects have also been documented to become operational at other stages of development (e.g. early to middle childhood or late childhood to adolescence) (Scourfield et al, 2003; van der Valk et al, 2003).

Studies comparing genetic and environmental influences operating at the extreme end of the depression spectrum with those in the normal range have been relatively consistent in showing larger shared environmental effects among individuals with more severe levels of depression, and an accompanying decrease in genetic effects although these differences have rarely reached significance (Deater-Deckard et al, 1997; Eley, 1997;

Rende et al, 1993; Rice et al, 2002). Yet the role of age and sex on these differences are unclear, with some suggestion that this pattern of results may only apply to adolescents (Gjone & Stevenson, 1996; Rice et al, 2002), but are similar for males and females.

Taken together these studies cement the notion that although genetics has the potential to supply epidemiological findings on depression with an aetiological level of explanation, the complex interplay between age, sex, development and severity of symptoms needs to be clarified first. Hence the goal of this Chapter is to explore the nature of genetic effects on depression with regard to these issues using the child and adolescent samples described in Chapter 3. First, age and sex differences in genetic and environmental effects on depressive symptoms occurring in childhood and adolescence were examined by cross-sectional comparisons of these influences at different ages and between males and females. Second the longitudinal design of each sample afforded the possibility of investigating stable genetic and environmental influences, contributing to developmental continuity, and new genetic and environmental influences, impacting upon change. Finally, the aetiology of extreme groups was investigated in each sample. Addressing these questions in the current samples not only permits clarification of previous findings, but comparing results across children and adolescents allows inferences on the expression of genetic and environmental effects in different developmental periods. Thus the role of stable and new genetic and environmental factors in contributing towards phenotypic continuity and change, and the causes of more severe forms of depression can be examined separately in each age group.

4.3. Methods

4.3.1. Participants and Measures

The current analyses used self-reported depression symptom data collected at Waves 1 and 2 of the ECHO childhood sample and Waves 1, 2 and 3 of the G1219 adolescent

sample. The child sample reported symptoms using the Children's Depression Inventory (Kovacs, 1981) whereas the adolescent sample completed the short Mood and Feelings Questionnaire (Angold et al, 1995). A four-point scale was used at waves 1 and 2 of G1219 whilst a three-point scale was used at wave 3 (Section 3.3.1.3).

4.3.2. Statistical Analysis

Data preparation was conducted using the Statistical Package for Social Sciences (SPSS: Kinnear & Gray, 2000). Data analysis, which consists of two stages of basic descriptive and model-fitting analyses, was performed using Mx. This software can simultaneously control for any non-independence of data due to clustering effects among family members, as well as incorporate sampling weights and selection variables in descriptive and model-fitting analyses. Basic descriptive analysis involved testing group differences within sex (males and females) and zygosity (MZ, DZ and FS), and were computed by fitting a saturated model in Mx (see Section 3.2.3.2). Model-fitting to raw twin and sibling data included univariate models with sex-specific effects to identify genetic and environmental effects on depression symptoms; multivariate longitudinal analyses examining genetic and environmental contributions to developmental continuity and change; and univariate analyses of the genetic and environmental aetiology of extreme groups. Given the different sampling procedures and study designs of the G1219 and ECHO samples, modelling techniques differed somewhat between these. Weighting variables to account for any initial response bias and subsequent attrition were included in G1219 (see Section 3.3.1.2), whilst for all ECHO analyses, the selection variable was included to correct for the selected nature of the sample (see Section 3.3.2.2). Both these additions are documented in Mx scripts used for these analyses, and example scripts are listed in Appendix B.1 to B.4. Other variations in modelling techniques between the samples are described in subsequent sections.

4.3.2.1. Descriptive analyses

Saturated models estimate the maximum number of parameters to describe the variances, covariance and means of all measured variables from raw data, and are typically used in the calculation of relative measures of model-fit, such as Chi-square (χ^2) of genetic models. A second usage of this output is to perform descriptive analyses on the summary statistics obtained (Appendix B.1). As these are specified separately for different sex-specific zygosity groups (MZ males, DZ males, MZ females, DZ females, DZ-opposite sex, FS males, FS females and FS opposite-sex), differences between males and females or in different twin and sibling zygosity types can be tested. Saturated models were fitted separately to depression data at each Wave of the G1219 and ECHO studies.

Sex differences were tested by comparing Model 1a which estimates one mean for males and one mean for females, with Model 1b which estimates one mean across the whole sample. Zygosity differences were ascertained by comparing Model 2a, which estimates zygosity-specific means among males and zygosity-specific means among females, with Model 2b which equates means across zygosity group (i.e. one mean for males and one mean for females). Thus this comparison tests for differences between zygosity groups, independent of any sex differences that are present. As Models 1a and 1b, and Models 2a and 2b are nested within one another, any significant deterioration in fit between them, indexed by the Chi-square (χ^2), which is generated by differences in log likelihood (-2LL), reflects possible differences in the means between males and females or zygosity groups.

A third test necessitated by the inclusion of siblings in the G1219 sample was the equality of within-pair covariances between full sibling pairs and DZ pairs given that the covariance between these two groups are modelled similarly in subsequent genetic

models (see Section 3.2.3.1). Any differences between them may signify a twin specificity effect that may inflate (or attenuate) within-pair similarities among twins but not in siblings. To ascertain such differences, Model 3 equated the correlations between DZ males and FS males, DZ females and FS females, and opposite sex DZ twins and opposite sex full siblings. This was assessed against the full saturated model which does not include these equality constraints. Any significant worsening in fit was attributed to unequal within-pair covariance between DZ and FS pairs.

Phenotypic correlations between variables can also be computed in the saturated model, by examining correlation matrices between two or more specified variables, and equating these across sex-specific zygosity groups. Thus associations with age and inter-correlations between depression measures at different time-points were obtained in Mx. The level of significance of a correlation is tested by excluding it from the model, and assessing the associated deterioration in fit. Of note, age trends were only conducted in the G1219 adolescent sample, given that the ECHO child sample consisted of twins born in the same year, and therefore there was reduced variation in age.

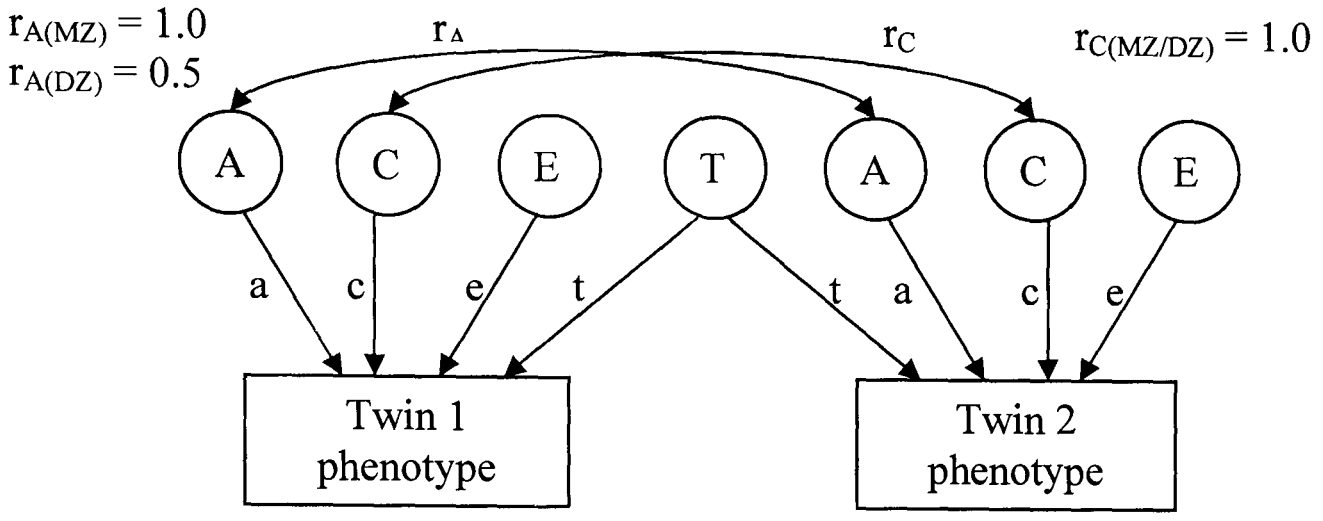
All descriptive analyses were performed on raw scores of depression. As the distributions of scores at Waves 1, 2 and 3 of the G1219 sample were positively skewed, a log transformation [ln(x+1)] was applied to approximate normality.

4.3.2.2. Univariate genetic models

Univariate genetic models decompose the variance of the depression measures into genetic (a^2), shared environmental (c^2) and non-shared environmental (e^2) effects based upon the relative differences between MZ within-pair covariances and DZ/FS within-pair covariances. This basic model can be extended to include a fourth source of latent factor depicting a twin similarity (t^2) effect (Figure 4.1). This factor is by definition specified to account for within-pair similarity among MZ and DZ twins over and above

that between siblings. As such it was only included in the model if the phenotypic similarity among DZ twins is not demonstrated to be comparable to that between full sibling pairs, as shown by earlier descriptive analyses.

Figure 4.1: Univariate genetic analysis of twin data with Twin Similarity effects



To estimate the twin similarity effect, the equations summarising the expected within-pair covariances for MZ and DZ twins are re-defined to include this additional term:

$$r_{MZ} = a^2 + c^2 + t^2$$

$$r_{DZ} = \tfrac{1}{2}a^2 + c^2 + t^2$$

Similarly, the variance of each twin's score ($V_{P(twin)}$) reflects this variance component:

$$V_{P(twin)} = a^2 + c^2 + e^2 + t^2$$

In contrast sibling scores and their within-pair similarity are not influenced by a twin similarity effect, thus the equations summarising the variance of each sibling's score ($V_{P(sibling)}$) and the expected within-pair covariance remain the same:

$$r_{FS} = \tfrac{1}{2}a^2 + c^2$$

$$V_{P(sibling)} = a^2 + c^2 + e^2$$

Including these alterations within the Mx script can allow for the quantification of a twin similarity effect. The level of significance of this parameter is tested by excluding it from the model, and assessing the change in model-fit.

Sex differences in the nature of genetic and environmental influences on depressive symptoms can also be incorporated in univariate genetic models (Neale & Maes, 2001).

These can be quantitative (differences in the *size* of genetic and environmental factors), qualitative (differences in the *type* of genetic and environmental factors) or scalar (differences in the variance of scores), and are tested by comparing five different sex-limitation models, which vary in their assumptions and specifications of the genetic and environmental parameters in male and female groups. Model 1 assumed both quantitative and qualitative sex differences by allowing parameter estimates to differ between males and females, and permitting the genetic relatedness index, usually specified as 0.5 for all DZ and full sibling pairs, to deviate from this value for opposite-sex twins and siblings. Thus this model tests for differences in the overlap in genetic variance shared between opposite sex twins and siblings, compared to same-sex pairs, thus potentially implicating variation in the types of genetic factor influencing male and female reported depression. Similarly, Model 2 examined qualitative differences in the type of shared environmental factors between males and females by allowing the shared environmental relatedness index between opposite-sex twins and siblings to deviate from the specified value of 1.0. This model also included quantitative sex differences. Model 3 assumed quantitative sex differences in the *size* of genetic and environmental parameters, by allowing these to differ between males and females. Model 4 tested for *variance* differences between males and females on each measure by including a scalar term that was only applied to male twin and sibling data. Finally Model 5 specified no sex differences by equating parameter estimates and variances across males and females. The model of best-fit is typically chosen as that with the lowest fit statistic, calculated through comparison with a saturated model. However when models are nested, selection of the best-fitting model is also dependent on whether it shows a significant change in fit compared to its preceding model (e.g. Model 4 vs. Model 5). Thus in the case where Model 4 has the lowest fit statistics (χ^2, AIC, RMSEA) but Model 5 does not show a significant change in fit compared to Model 4, Model 5 should

be selected as the model of best-fit. Depending on the chosen model, sex effects in the pattern of genetic and environmental influences on depression can be inferred.

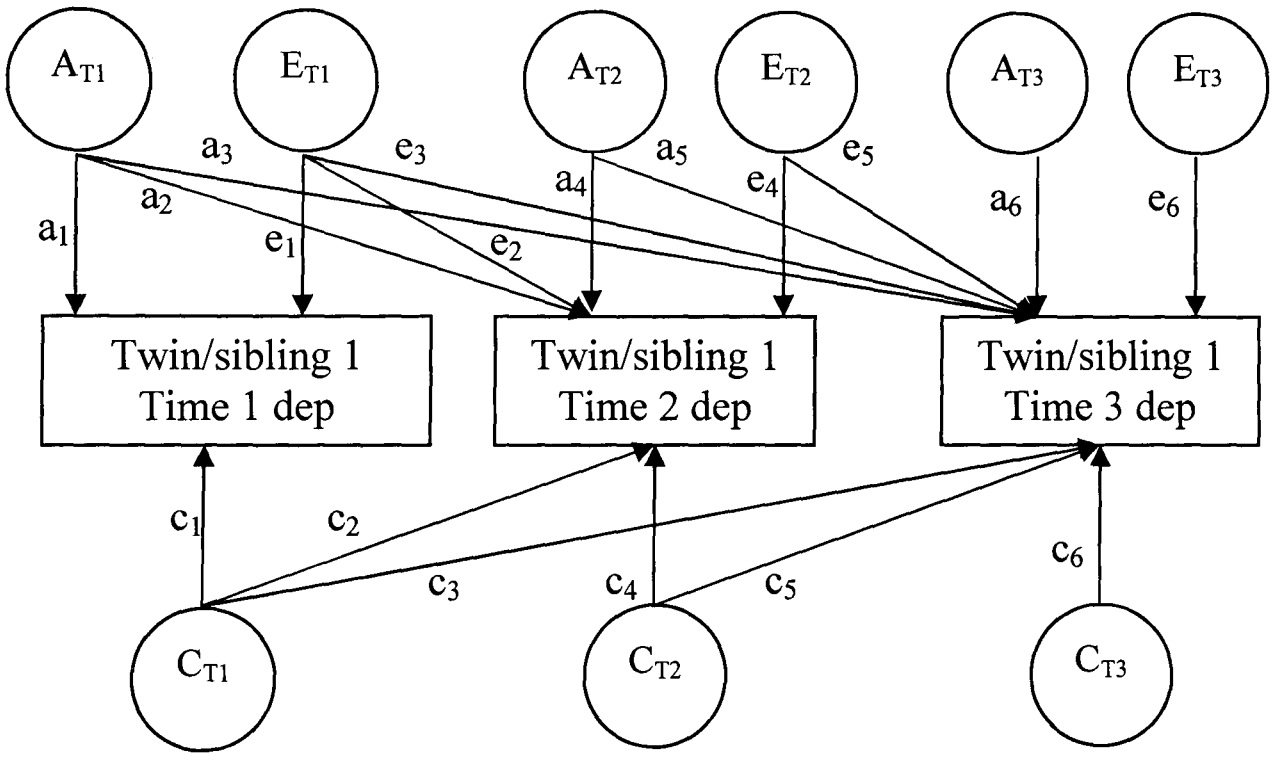
Univariate genetic models incorporating sex-specific effects were examined for all three depression measures collected from the G1219 sample (Appendix B.2). Due to the smaller sample size of the ECHO study and therefore lower power to detect sex differences, the different sex-limitation models were not considered for these data. Instead a single set of results equated across males and females are presented for the whole sample in all genetic models. Twin similarity effects, which only apply to twin and sibling data of the G1219 study, were examined if differences in within-pair covariance between DZ twins and full sibling pairs were found. A twin specificity effect may inflate (or attenuate) within-pair similarities among twins but not in siblings.

All analyses were performed on age-regressed, and where appropriate log-transformed depression scores, to minimise any mean effects associated with age and to correct for positive skewness respectively. Of note, removing the main effects of age is particularly important in the adolescent sample due to differences in age between members of a sibling pair. This could artificially decrease their within-pair similarity relative to that of the same aged twin pairs. To minimise mean differences between sex and zygosity groups, means of these measures were modelled separately for each sex-specific zygosity group in the raw data genetic models. Cross-sectional comparisons between parameter estimates obtained from each time-point from the two samples were used to infer age-related trends in genetic and environmental parameters. Fit statistics for univariate models were calculated from saturated models, which estimate summary statistics to describe the means, variance and covariance of one measured variable collected from each twin or sibling.

4.3.2.3. Multivariate models examining change and continuity

Multivariate models decompose the covariance between measures into genetic, shared and non-shared environmental components, by using the ratio of MZ to DZ/FS cross-sibling cross-trait covariances (i.e. variable 1 of one sibling with variable 2 in the co-sibling) (Neale et al., 2001). A cholesky decomposition of three measured variables partitions additive genetic effects (a^2), shared environmental effects (c^2) and non-shared environmental effects (e^2) into three sets of factors (Figure 4.2). A_1, C_1 and E_1 influence all three variables, A_2, C_2 and E_2 influence the second and third variables and A_3, C_3 and E_3 influence the third variable only. Although any possible ordering of the variables explains the variance-covariance matrix between variables equally well, the order can influence interpretation of the results.

Figure 4.2: Multivariate genetic analysis of longitudinal twin and sibling data for one member of a twin/sibling pair



With longitudinal designs, the variables are typically ordered according to the specific time sequence with which they were collected, thus justifying inferences of causality in the results. In particular, as 'stable' genetic and environmental influences contributing to the continuity of phenotypes across all three time-points (A_1, C_1 and E_1) can be

distinguished from 'new' aetiological influences that become operational at time 2 (A_2, C_2 and E_2) and time 3 (A_3, C_3 and E_3), genetic and environmental continuity and change can be assessed. For example the proportions by which a_3 and a_5 account for the total genetic variance on depression at time 3 ($a_3 + a_5 + a_6$) reflect the extent to which 'stable' genetic factors are influential in depression, whereas the corresponding proportion that a_6 explains of the total genetic variance represents the effect of 'new' genetic influences. Thus the relative proportions of stable and new influences at each time-point can be calculated to infer when developmental factors become effectual.

A Cholesky decomposition of three factors was fitted to the depression data from Waves 1, 2 and 3 of the G1219 study to examine whether stable and new genetic and environmental influences explained continuity in symptoms during adolescence. A three factor model jointly analysing Waves 1 and 2 depression data with the age 7 anxiety selection variable, was tested in the ECHO study (Appendix B.3). This examined any longitudinal overlap in genetic and environmental influences between anxiety symptoms and later depressive symptoms, and genetic and environmental contributions to developmental continuity and change in depressive symptoms during childhood.

Any significant sex differences in genetic and environmental influences that emerged from earlier analyses were included in these models, by specifying different parameters for males and females. Twin similarity effects were only included in these analyses if they reached significance in univariate analyses in the G1219 sample. Analyses were again performed on age regressed depression scores, and where appropriate, measures were first corrected for positive skewness. Means of these measures were estimated separately for each sex-specific zygosity group to allow for mean differences between sex or zygosity groups. Fit statistics for each model were calculated from saturated models, which estimated summary statistics describing the means, variance and covariance of three measured variables from each twin/sibling.

4.3.2.4. Univariate models of extreme scoring individuals

Estimates of group heritability and group environmental influences that characterise extreme scoring individuals can be derived using a regression model (DeFries & Fulker, 1985; DeFries & Fulker, 1988). This approach assumes a continuous distribution of phenotypic scores of which extreme scoring individuals, defined as 'probands', are those who score above a selected threshold. The differential extent to which MZ and DZ (or FS) co-twins regress away from the proband mean towards the population mean provides a test of genetic influence. That is, given that a phenotypic measure is heritable, the scores of MZ co-twins are expected to fall closer to the proband mean (and thus further from the population mean) compared to the scores of co-twins or co-siblings of DZ or full sibling pairs. The scores of co-twins (C_M) can therefore be predicted as a function of proband means (P_M) and the coefficient of genetic relatedness (R) between the co-twin and proband pair, such that R is 1 for MZ twins and is 0.5 for DZ twins and full siblings. This can be summarised as a regression-based equation:

$$C_M = B_1P + B_2R + A$$

where A is the regression constant, the regression weight B_1 corresponds to the partial regression of the co-twin score on the proband score and is therefore an indicator twin resemblance independent of zygosity, and B_2 is the partial regression of the co-twin score on the coefficient of genetic relatedness and reflects the differential regression of the co-siblings of different zygosity types. In fact, following a simple transformation of the data, in which the scores are expressed as a deviation away from the population mean, B_2 becomes a group heritability estimate and group shared environment is calculated as the difference between the MZ co-twin mean and group heritability. The equation for transformation is:

$$C_{Score} - \mu_{POP} / \mu_{PRO} - \mu_{POP}$$

where C_{Score} is an individual's score, μ_{POP} is the population mean, and μ_{PRO} is the proband mean. Thus these analyses comprise an analysis of mean differences between zygosity groups (MZ, DZ and FS) rather than an analysis of individual differences.

Although the original formulation of this model is based upon the use of a simple regression method, it can be easily re-framed within model-fitting analyses that utilise maximum likelihood methods to obtain parameters of best-fit from the transformed data (Purcell & Sham, 2003). Specifically the structure of the expected means is altered to reflect each individual's expected score as a function of their co-twin's proband status and their genetic and shared environmental relatedness, re-defined as:

$$M_{MZ} = [a^2 + c^2] \times [p_2, p_1]$$

$$M_{DZ/FS} = [\tfrac{1}{2}a^2 + c^2] \times [p_2, p_1]$$

for MZ and DZ or full siblings respectively, where the proband status of the co-twin/sibling is represented by the vector $[p_2, p_1]$ and the extent to which co-twin and proband pairs share the same genes is reflected in the first vector. An additional option available to the model-fitting approach is the inclusion of opposite sex twin and sibling pairs, and the facilitation of quantitative sex differences to be tested. As before, these differences are examined by comparing Model 1, which allows for different estimates for males and females with Model 2, which equates these estimates. A significant drop in χ^2 between them indicates sex differences in the size of parameter estimates.

This model was fitted to transformed data in both G1219 and ECHO samples (Appendix B.4). As G1219 is an unselected sample, the observed depression scores are thought to form a continuum, upon which probands were selected as those scoring one standard deviation above the mean, in line with previous studies (e.g. Eley, 1997; Rice et al, 2002; Deater-Deckard et al, 1997). For transformation purposes the population mean was calculated based on the mean of the whole sample. Probands for extreme

depression scores in the ECHO sample were also selected as individuals scoring one standard deviation above the mean. However as ECHO is already a selected sample, consisting of 247 twin pairs where at least one of the twins scored in the top 15% on anxiety scores assessed at age 7, and 53 control pairs where neither twin's score fell in this deviant group, the population mean had to be re-adjusted to take into account the over-representation of anxiety proband pairs. To correct for ascertainment, the population mean was calculated using depression scores from 62 twin pairs, including the 53 control twin pairs, originally selected as representing the bottom 85% of anxiety scores (53/62 = 85%), and a random selection of 9 anxiety proband pairs, to represent those falling in the top 15% of anxiety scores at age 7 (9/62 = 15%). The re-adjusted population mean was used in the transformation of scores. A similar procedure was used for Wave 2 transformations, such that the population mean was calculated on the basis of the 39 controls pairs collected to date (39/46 = 85%) which has been collected to date, and a random selection of 7 proband pairs (7/46 = 15%).

Transformation of the data was performed on age-regressed symptom scores. To assess the fit of these models, a saturated model which estimates separate means and variances across different zygosity groups was used.

4.4. Results

4.4.1. Descriptive analyses

Tables 4.1a and 4.1b present the means, standard deviations, sample sizes and correlations of twin and sibling pairs across males and females for depression symptoms in the ECHO and G1219 samples respectively. Results from testing mean differences between males and females and between zygosity groups, and differences in within-pair covariances between DZ and full siblings using a saturated model are summarised in Table C.1a and C.1b (Appendix C). Comparison in the change of fit between Models 1a

and 1b, which respectively estimate separate means for males and females or equate them, indicated no significant sex differences in the ECHO sample at Wave 1 or 2 (mean = 8.77 and 6.84 for females in Waves 1 and 2, and 9.84 and 7.84 for males in Waves 1 and 2). However similar comparisons showed significant sex differences in depression symptom scores at all three time-points of the G1219 sample, with females consistently reporting more symptoms compared to males (mean =7.35, 8.92, 7.05 for females in Waves 1, 2 and 3 respectively, and 6.11, 6.54, 4.96 for males, for Waves 1, 2 and 3 respectively).

Table 4.1a: Data for depression scores at Waves 1 and 2 in the ECHO dataset in MZ and DZ pairs (SD = standard deviations; N = number of participants; r = correlation)

	MZ twins		**DZ twins**			
	M	**F**	**M**	**F**	**M**	**F**
					Opposite-sex	
Wave 1 Depression: 8 years (mean = 8 years 6 months)						
Mean	9.25	8.40	10.71	8.59	9.51	9.60
SD	6.93	6.84	6.56	6.62	7.01	7.10
N[a]	79	111	56	101	113	113
R	0.32		0.19			
Wave 2 Depression: 10 years (mean = 10 years 5 months)						
Mean	8.04	6.03	8.46	7.48	5.97	6.24
SD	4.99	6.04	5.23	4.72	5.57	6.89
N[a]	48	82	38	76	64	64
R	0.34		0.30			

[a] This refers to the number of individuals

MZ and DZ twins in the ECHO sample scored comparably on depression measures at both Waves. However significant mean differences between zygosity groups emerged at each Wave in the G1219 sample in both males and females, with full siblings reporting more symptoms compared to twins. Finally there were differences in within-pair

covariance between DZ and full siblings at Waves 1 and 3, with greater correlations (and thus phenotypic similarity) among DZ twins compared to full siblings.

Table 4.1b: Data for depression scores at Waves 1, 2 and 3 in the G1219 dataset in MZ, DZ and FS pairs (SD = standard deviations; N = number of participants; r = correlation)

	MZ twins		**DZ twins**				**Full Siblings**			
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
					Opposite-sex				Opposite-sex	
G1219 Wave 1 Depression: 12-19 years (mean = 14 years 5 months)										
Mean	5.75	6.72	5.84	7.14	6.55	7.39	6.06	9.13	7.53	8.22
SD	4.85	5.78	4.85	6.19	5.55	5.82	5.00	6.27	5.79	6.66
N[a]	399	476	328	437	553	553	212	250	183	182
r	0.52	0.57	0.33	0.49	0.34		0.22	0.14	0.27	
G1219 Wave 2 Depression: 12-21 years (mean = 15 years)										
Mean	5.84	8.03	6.92	8.77	6.99	9.05	6.73	10.98	8.03	10.27
SD	4.71	6.99	5.58	7.22	5.84	6.73	5.16	7.73	6.17	7.84
N[a]	313	392	250	374	324	331	104	181	114	133
r	0.30	0.50	0.13	0.39	0.24		0.21	0.21	0.32	
G1219 Wave 3 Depression: 14-23 years (mean = 17 years 8 months)										
Mean	4.32	6.42	5.55	7.61	5.23	7.08	5.20	7.34	5.31	7.16
SD	4.22	5.41	5.32	5.85	4.48	5.48	4.79	5.37	5.24	5.05
N[a]	175	267	131	262	197	223	50	97	60	81
r	0.43	0.33	0.27	0.32	0.25		0.19	0.01	0.15	

[a] This refers to the number of individuals

Phenotypic correlations between age and depression symptoms assessed at each time-point in the adolescent sample were modest: r = -0.03 (p = n.s.) for Wave 1, r = 0.06 (p < 0.01) for Wave 2 and r = 0.01 (p = n.s.) for Wave 3. Mean effects associated with sex, zygosity and age were controlled for in subsequent genetic models by regressing out the effects of age, and modelling means separately across different sex-specific zygosity

groups. Greater within-pair covariance among DZ twin pairs compared to full siblings was examined further by including a twin similarity effect in univariate genetic models.

4.4.2. Univariate Models of Depression

Given that DZ twins had a greater within-pair covariance compared to full siblings in the G1219 sample, a twin similarity effect was estimated first in univariate genetic models of Waves 1 and 3 depression variables. Removing this latent factor from the model did not result in changes of fit at either Wave: $\Delta\chi^2(1) = 0.00$ (p = n.s.) for Wave 1 and $\Delta\chi^2(1) = 0.00$ (p = n.s.) for Wave 3. This suggests that twins do not share more similar environments, which result in greater resemblance for depressive symptoms, compared to siblings. Thus this parameter was not considered in subsequent analyses.

Sex effects in genetic and environmental parameters of depression in the G1219 adolescent sample were examined by comparing five univariate models, as presented in Table C.2 (Appendix C). A model allowing for variance differences but not in parameter estimates between males and females was of best fit to Waves 1 and 2 depression data. The model with no sex-effects in variance or parameter estimates fit better to Wave 3 depression. Due to less power available for the detection of sex effects in the ECHO sample, no sex-effects were included in the univariate model examined at both Waves 1 and 2. As such a single set of parameters for males and females was estimated for both samples and are presented in Table 4.2 with summary fit statistics.

Results are presented in order of the age of when data were collected across samples so as to facilitate cross-sectional comparisons of parameter estimates. This revealed a general pattern of increasing genetic effects with age. Whilst significant genetic influences emerged at all time-points in the adolescent sample accounting for approximately 30-40% of the variance, these were smaller and non-significant in the child sample, indicated by confidence intervals that overlapped with zero. In contrast,

shared environmental effects were found to decrease across age, such that these influences were more important in late childhood (ECHO Wave 2) and early adolescence (G1219 Wave 1), but became smaller by mid-adolescence (G1219 Wave 2) and negligible by late-adolescence (G1219 Wave 3). Non-shared environmental effects were substantial during both childhood and adolescence. Of note, although neither genetic nor shared environmental effects were significant for the Wave 1 ECHO depression data, a model excluding both variance components, resulted in a significant deterioration in fit ($\Delta\chi^2(4) = 23.14$ ($p < 0.001$). This suggests that familial factors are important to depression symptoms at this age but power to distinguish between genetic and shared environmental explanations is limited.

Table 4.2: Summary model-fitting statistics of univariate genetic models of depression measures in ECHO and G1219. Parameter estimates with 95% confidence intervals show proportions of variance due to additive genetic (a^2), shared environmental (c^2) and non-shared (e^2) environmental influences

	Proportions of variance due to:		
	a^2	**c^2**	**e^2**
ECHO: Wave 1 Depression	16 (0-45)	13 (0-35)	71 (54-85)
-2LL = 29473.29, df = 10963, $\chi^2(38) = 49.11$, p = 0.11, AIC = -26.89, RMSEA = 0.03			
ECHO: Wave 2 Depression	1 (0-29)	27 (5-40)	72 (58-86)
-2LL = 28807.87, df = 10762, $\chi^2(38) = 43.87$, p = 0.24, AIC = -32.13, RMSEA = 0.03			
G1219: Wave 1 Depression	45 (32-58)	19 (9-29)	36 (31-41)
-2LL = 9529.34, df = 3507, $\chi^2(20) = 34.64$, p = 0.02, AIC = -5.36, RMSEA = 0.02			
G1219: Wave 2 Depression	36 (17-53)	10 (0-25)	53 (46-61)
-2LL = 6229.44, df = 2491, $\chi^2(20) = 31.98$, p = 0.04, AIC = -8.02, RMSEA = 0.02			
G1219: Wave 3 Depression	45 (22-31)	0 (0-16)	55 (47-65)
-2LL = 3239.77, df = 1523, $\chi^2(21) = 17.36$, p = 0.69, AIC = -24.64			

4.4.3. Multivariate Models examining change and continuity

Phenotypic correlations between Waves 1 and 2 indicate strong continuity of depressive symptoms across time in childhood. The correlation between Waves 1 and 2 was 0.45 ($p < 0.001$). However correlations between anxiety at age 7 and depression symptoms assessed at Waves 1 and 2 were modest, at 0.10 ($p < 0.05$) and 0.14 ($p < 0.01$). Strong stability of depressive symptoms in the G1219 sample was also found. The correlation between Waves 1 and 2 was 0.58 ($p < 0.001$), between Waves 2 and 3, 0.45 ($p < 0.001$) and between Waves 1 and 3, 0.40 ($p < 0.001$).

Cholesky decomposition models were performed on longitudinal data from the ECHO and G1219 samples to assess the effects of stable and new genetic and environmental factors. ECHO depression measures were analysed jointly with the age 7 selection variable to control for ascertainment biases. Summary model-fitting statistics and parameter estimates of these models are presented in Table 4.3. This table is divided into effects of three sets of factors, emerging across time. A_1, C_1 and E_1 occur at Time 1 and influence measures at all three time-points; A_2, C_2 and E_2 emerge at Time 2 to influence measures at Time 2 and 3; and A_3, C_3 and E_3 emerge at Time 3, and are specific to the measure at that time-point. As there were no sex differences in the size of genetic and environmental parameters in the G1219 adolescent sample, a single set of parameters was presented for the whole sample.

Both models show good fit to the data. The total estimated genetic and environmental effects on each depression measure can be obtained by summing the contributions of common and specific components. As such, the estimated heritability of depression at Wave 1 of the G1219 adolescent sample is A_1, at Wave 2 is $A_1 + A_2$ and at Wave 3, $A_1 + A_2 + A_3$. In general the total genetic and environmental effects estimated for each depression measure in these multivariate models are consistent with those derived in univariate genetic models. The most notable differences was the shared environmental

component of Wave 1 G1219 depression, which is non-significant in the current multivariate model (9%) as indicated by the overlap of confidence intervals with zero, whereas in univariate models, it was estimated at 19%. Such slight variations in parameter estimates may be due to additional information available in cross-twin/sibling, cross-measure covariance.

Table 4.3: Summary model-fitting statistics and parameter estimates with 95% confidence intervals of multivariate longitudinal genetic models of depression between Waves 1 and 2 and age 7 data in ECHO and Waves 1, 2 and 3 in G1219.

	Time 1 factors			**Time 2 factors**			**Time 3 factors**		
ECHO	**A_1**	**C_1**	**E_1**	**A_2**	**C_2**	**E_2**	**A_3**	**C_3**	**E_3**
Age 7	48	18	34						
Anxiety	(41-55)	(12-23)	(32-36)						
Wave 1	1	3	0	15	11	70			
	(0-9)	(0-25)	(0-10)	(0-42)	(0-32)	(54-86)			
Wave 2	0	15	0	5	10	4	0	0	66
	(0-6)	(0-36)	(0-2)	(0-34)	(0-34)	(1-11)	(0-16)	(0-17)	(53-78)
-2LL = 30340.25, df = 11319, $\chi^2(87) = 120.73$, p = 0.01, AIC = -53.27, RMSEA = 0.04									
	Time 1 factors			**Time 2 factors**			**Time 3 factors**		
G1219	**A_1**	**C_1**	**E_1**	**A_2**	**C_2**	**E_2**	**A_3**	**C_3**	**E_3**
Wave 1	58	9	33	---	---	---	---	---	---
	(40-71)	(0-23)	(28-40)						
Wave 2	26	5	4	10	7	48	---	---	---
	(12-43)	(0-24)	(2-8)	(1-21)	(0-14)	(43-55)			
Wave 3	16	1	3	27	1	1	0	0	51
	(5-30)	(0-14)	(1-7)	(5-35)	(0-10)	(0-4)	(0-22)	(0-11)	(44-59)
-2LL = 11559.63, df = 4982, $\chi^2(149) = 183.92$, p = 0.03, AIC = -114.08, RMSEA = 0.02									

Of note, as with univariate analyses, genetic and shared environmental parameters derived in multivariate genetic modelling of ECHO data overlap with zero. Interpretation is thus based upon the effect size of estimates. These results show that

phenotypic continuity in emotional (both anxiety and depression) symptoms is due mainly to stable shared environmental influences, emerging at age 7 (C_1) and at age 8 (C_2). Shared environmental effects, which influence anxiety symptoms at age 7 (C_1), also contribute towards Waves 1 and 2 depression symptoms. Of the total shared environmental variance at Waves 1 and 2, these effects account for 21% (3 / 3+11) and 60% (15 / 15+10) of the variance respectively. A second set of shared environmental influences, which primarily influence depression symptoms at Wave 1 (age 8) (C_1), is also involved in Wave 2 symptoms, explaining 40% of the total shared environmental variance at this latter time-point. Whilst there are negligible shared genetic effects between anxiety at age 7 and later depression symptoms, there are some new genetic sources emerging at Wave 1, which contribute albeit minimally towards Wave 2 symptoms. Non-shared environmental effects are generally specific to each time-point.

In the adolescent sample, a stable genetic factor (A_1) influences depression at all three time-points, accounting for 72% (26 / 26+10) and 37% (16 / 16+27) of the total genetic variance at Waves 2 and 3 respectively. A new genetic factor emerges at Wave 2, which contributes to 63% of the total genetic variance at Wave 3 as well. No more new significant genetic influences are apparent by Wave 3. There is a common shared environmental factor between Waves 1 and 2 although the contribution of this factor to depression at both time-points is non-significant. Non-shared environmental effects although significant, are generally specific to each time-point.

4.4.4. Univariate extremes analysis

Summary fit statistics and parameter estimates of the analysis of extremes scoring individuals are presented in Table 4.4 for ECHO and G1219. Quantitative sex effects on univariate estimates of genetic and environmental parameters in the G1219 adolescent sample were examined by comparing two models. Fit statistics of these models are

presented in Table C.3 (Appendix C). A model with no sex differences in genetic and environmental parameter estimates best fit Waves 1 and 3 depression data whereas a model allowing parameter estimates to differ for males and females fit the data best at Wave 2. As seen in Table 4.4, males showed less genetic and shared environmental effects compared to females. Due to the lack of power available for the detection of sex effects in the ECHO sample, these were not explored and a single set of parameters for the whole sample are presented in Table 4.4. Wider confidence intervals in the estimates of group heritability and group environmental effects indicate less power than that available in individual differences analyses to detect significant effects at the extremes.

Table 4.4: Summary model-fitting statistics and parameter estimates with 95% confidence intervals of extreme group analysis of depression at Waves 1 and 2 in ECHO and Waves 1, 2 and 3 in G1219. h_g^2, c_g^2 and e_g^2 refer to group heritability, group shared environment and group non-shared environment.

	Group genetic and environmental effects		
	h_g^2	**c_g^2**	**e_g^2**
ECHO: Wave 1 Depression	1 (0-49)	28 (0-40)	71 (50-83)
-2LL = 856.43, df = 566, $\chi^2(11) = 5.53$, p = 0.91, AIC = -16.47			
ECHO: Wave 2 Depression	11 (0-75)	46 (0-68)	44 (18-63)
-2LL = 483.94, df = 368, $\chi^2(11) = 8.09$, p = 0.71, AIC = -13.91			
G1219: Wave 1 Depression	35 (0-65)	18 (0-36)	47 (33-60)
-2LL = 6519.76, df = 3072, $\chi^2(20) = 30.76$, p = 0.06, AIC = -9.24, RMSEA = 0.05			
G1219: Wave 2 Depression			
Males	4 (0-34)	11 (1-27)	84 (63-94)
Females	17 (0-55)	35 (8-56)	48 (32-62)
-2LL = 4346.92, df = 2352, $\chi^2(18) = 32.83$, p = 0.02, AIC = -3.17, RMSEA = 0.07			
G1219: Wave 3 Depression	13 (0-54)	26 (0-42)	61 (43-74)
-2LL = 2169.65, df = 1394, $\chi^2(20) = 18.80$, p = 0.54, AIC = -21.20			

These estimates are of most interest when compared to those obtained in the normal range (Table 4.2). In general, there is a noteworthy pattern of slightly larger estimates for group shared environmental effects in the selected extreme groups compared to those obtained in individual differences analyses. This was true for both the child and adolescent sample, although these differences did not reach significance in the child sample. Interestingly, high scoring females at Wave 2 and high-scoring males and females at Wave 3 of the G1219 adolescent sample show significant shared environmental effects, but do not show this pattern in the normal range.

There is also a pattern of decreasing genetic effects in individuals reporting extreme scores. Whereas genetic influences were significant in explaining individual variation at Waves 1, 2 and 3 of the G1219 sample, these are smaller and often non-significant when estimated in extremes analyses. Similarly group heritability indices were also notably smaller at the extremes, compared to the normal range at Wave 1 the ECHO sample data. This difference was not present for Wave 2 data.

4.5. Summary

The current study addressed three different issues relating to the role of genetics and the environment on depression symptoms reported by children and adolescents. These included the effects of age and sex on genetic and environmental contributions to depression, the role of genetic and environmental influences in governing developmental continuity and change and the genetic and environmental effects in individuals reporting extreme levels of depression. Studying these issues separately in children and adolescents provided an opportunity to further delineate developmental differences in the nature of genetic and environmental influences on depression.

Results were generally in keeping with existing literature. Previous epidemiological findings of an increased preponderance of depressive symptoms among females in

adolescence but not in childhood were replicated by descriptive analyses. However univariate genetic models incorporating sex differences in the adolescent sample showed that males and females did not differ significantly in the *size* or *type* of genetic and environmental factors towards depression symptoms but instead showed variance differences. Sex-specific effects in genetic and environmental factors were not explored in the child sample due to power limitations. Parameter estimates from univariate models of depression data from each sample at different time-points supported a trend of increasing genetic effects from late childhood onwards, reaching a peak in adolescence. Simultaneously a reduction in shared environmental effects was also observed, such that these influences were maximal in late childhood (age 10).

Multivariate models examining longitudinal continuity of depression data showed that 'stable' genetic influences operational in early adolescence accounted partly for the stability of symptoms across time, however there were also 'new' genetic effects operational at mid-adolescence, which were also involved in depression symptoms in late-adolescence. A somewhat different pattern of results was obtained in children. Shared environmental effects operational at age 7 influenced both concurrent anxiety symptoms and later depression assessed at ages 8 and 10. Furthermore newer shared environmental effects also emerged at age 8 to influence the phenotypic continuity of depression symptoms at age 10. New genetic effects were observed at age 8 but these were not particularly influential at age 10. Non-shared environmental influences were generally age-specific in both childhood and adolescence.

A pattern of increased shared environmental effects but attenuated genetic contributions was obtained in analyses of individuals reporting more severe levels of depression, a trend that was apparent in both childhood and adolescence. However as the confidence intervals of these estimates continue to overlap with those from the normal range such differences may not implicate significant departures in heritability or significant

amplifications in environmental effects amongst severe populations. Rather they indicate non-significant trends of larger contributions of the shared environment to extreme group membership in childhood and adolescence.

Whilst these results are largely consistent with previous trends, they need to be interpreted in the context of several limitations. First it was somewhat unexpected to obtain mean differences in the levels of depressive symptoms between full siblings and DZ twins in both males and females at all three time-points in the adolescent sample, with siblings reporting more symptoms compared to twins. Whilst previous research has not identified variations in the emotional development and problem behaviours of twins and singletons, this finding may indicate 'protective' effects associated with being a twin, against depressive symptoms. Another possibility is that twins with higher levels of depression were less likely to take part in the current study. Although such mean differences in symptom levels between twins and siblings do not necessarily imply differences in the causes of individual variation within each group, caution when generalising these results to non-twin populations should be endorsed.

A second set of limitations concerns the accuracy of the estimates of heritability and environmental effects derived from the genetic modelling procedures. First, the various genetic models tested in the current study did not incorporate effects associated with gene-environment correlation and interaction, which have been demonstrated to be important to depression symptoms in other studies (e.g. Eaves et al, 2003; Silberg et al, 2001) and in a subsequent Chapter of this thesis. Excluding these effects may inflate genetic and non-shared environmental parameters at the expense of shared environmental effects. Second there were wide confidence intervals obtained on many of the genetic and environmental parameter estimates, in particular for ECHO analyses and in more complex models requiring more statistical power. This suggests caution in interpreting results, and reinforces a need for further replication before solid conclusions

are drawn. Third it is possible that due to selective response and attrition biases the results reported in the current samples under-estimate environmental effects, in spite of the weighting system used. It is universally appreciated that the derivation of genetic and environmental effects is specific to the population studied, and any biases which may induce changes to the distribution of phenotypic scores will necessarily impact upon findings. Whilst these three limitations may well impact on the *exact* estimates of genetic and environmental parameters, there may be few, if any theoretical or practical implications of a 'true' heritability of 40% rather than 50% (Rutter, 2003).

A final limitation concerns interpretations of the analysis of high-scoring individuals. Selection of extreme groups within a non-clinical sample on a single dimension of mood-related symptoms may lead to a systematic bias in finding *no* differences between extreme group and individual differences estimates (Deater-Deckard et al, 1997). Thus non-significant departures in heritability and increases in shared environmental effects may be driven by this methodological artefact rather than indicating a lack of difference in aetiology. Nevertheless, these findings are similar to other studies, which have selected extreme individuals on other measures of depression and different thresholds. Moreover, results from a recent study of clinically recruited twins (Glowinski et al, 2003) did not show marked differences to those of community-based samples.

In summary the findings of the current Chapter form the basis for understanding the role of genetic effects in accounting for vulnerability to depression and the developmental trajectory by which these risks are expressed. The implications of this study in the context of the overall aims of this thesis are discussed in more detail in Chapter 8. The next Chapter explores two different pathways by which genetic risks, which are maximal in adolescence, may be expressed in this age range through interplay with environmental factors.

Chapter 5: Gene-Environment Interplay on Adolescent Depression Symptoms

5.1. Overview

Results from Chapter 4 suggest a pattern of age-related increases in genetic effects from childhood to adolescence. Furthermore, 'new' genetic effects may become operational during early and mid-adolescence, which subsequently account for developmental continuity of symptoms in late-adolescence. In comparison to shared environmental effects, which decrease across adolescence, non-shared environmental effects are consistently substantial, with 'new' factors emerging at different time-points during adolescence. The aim of this Chapter is to explore possible pathways by which genetic and environmental effects are expressed during mid-adolescence to create vulnerability towards depressive symptoms. In particular, two potential mechanisms by which genetic effects influence environmental risk exposure (gene-environment correlation) and increase susceptibility towards these risks (gene-environment interaction) are examined. Data collected from the G1219 adolescent sample at Wave 2 were first used to investigate genetic effects on exposure to negative life events and maternal punitive discipline, which represent two aspects of social risk. More importantly, the degree of overlap in genetic effects between environmental risks and depression symptoms was assessed. Next, the extent to which genetic and environmental effects on depression varied at different levels of negative life events and maternal punitive discipline whilst controlling for spurious effects of gene-environment correlation was addressed. Both environmental risk factors showed significant genetic effects, thus implicating gene-environment correlations. Moreover, there was significant overlap in genetic effects that were involved in each risk factor and depression symptoms, indicating that genetic risks on the phenotype may be expressed through the creation of environmental vulnerability.

Third, genetic effects on depression symptoms significantly increased as a function of life events and maternal punitive discipline, after controlling for gene-environment correlation. Whilst a 'common' genetic factor was involved in both gene-environment correlation and interaction with negative life events, genetic influences involved in correlation and interaction with maternal punitive discipline were distinct. Lastly non-shared environmental variance increased across levels of maternal punitive discipline.

5.2. Background

There is consistent evidence to support the role of both genetic and environmental factors in the precipitation of adolescent depression symptoms. Genetic influences are estimated to account for approximately 30-50% of the variance in depression symptoms assessed in this age range with the remaining variance mainly due to non-shared or individual-specific environmental effects (Eley, 2000). In the search for specific social risk factors, 'provoking agents' such as life events and chronic stressors, such as family relationships, may represent environmentally-transmitted risks on this phenotype (Goodyer, 1990). More recent studies in this area have moved beyond quantifying and specifying these individual factors, to considering the nature of their interplay in creating vulnerability towards adolescent depression. In particular, correlations and interactions between genetic and environmental factors may represent important risk mechanisms of depression (Eaves et al, 2003). Gene-environment correlations (r-GE) occur when there are increased frequencies of individuals with a certain genotype in a particular environment, such as when genetic factors influence exposure towards environmental conditions. Gene-environment interactions (GxE) arise when there is a differential effect of one variable on the outcome measure at varying levels of another variable. For example, when environmental risk effects vary as a function of genetic risk, or when genetic risks are expressed only in the presence of a social stressor.

Support for gene-environment interactions and correlations in adolescence come from a range of family and twin designs. These have demonstrated that many aspects of environmental risk including both provoking factors and chronic stressors show genetic influence (rGE), and moreover that these overlap with genetic factors of depression (e.g. Pike et al, 1996; Silberg et al, 1999; Rice et al, 2003). This suggests that genetic risks on depression are in part expressed through the creation of high-risk environments. Second there are findings suggesting that these social factors also moderate genetic effects on depression symptoms (GxE) (e.g. Silberg et al, 2001; Eaves et al, 2003).

Until recently, these processes have been studied relatively independently from one another albeit there being two important reasons for their joint consideration. The first concerns the validity of interaction effects. True interactions are premised on the assumption that the distribution of genotypes over the range of environmental conditions is random. This is easily violated if genotypic frequencies are higher in individuals of a particular environmental condition, such as when gene-environment correlation is present. Thus to prevent spurious findings of interaction, there is a need to control for simultaneous correlation which provides an equally plausible explanation for the observed effects. Second, there is some evidence to show that the same genetic and environmental factors may be involved in both correlations and interactions, indicating that these processes are not entirely independent and in fact co-exist.

The aim of the current Chapter was to simultaneously differentiate and assess the effects of both correlations and interactions between genetic effects on depression and two environmental risk factors: negative life events and maternal punitive discipline. In the first stage of analyses, genetic influences on both environmental risk measures were assessed, thus examining the presence of gene-environment correlation. Second, the extent to which genetic effects on negative life events and maternal punitive discipline also contributed towards depression was tested. This indicated whether there were

genetic correlations between each environmental risk and depression. Finally, moderation of genetic effects by negative life events and maternal punitive discipline was assessed using a novel modelling technique. As this model controls for spurious effects of genetic correlations between environmental risk measures and depression, it increases the validity of gene-environment interaction effects. It also allows verification of whether the same genetic and environmental factors were involved in both processes of interplay. A final and concurrent aim was to explore potential interactions between environmental effects. Specifically moderation of environmental variance by negative life events and maternal punitive discipline was addressed, based on suggestions that the presence of one social risk exacerbates effects of another (Goodyer, 1990).

5.3. Methods

5.3.1. Participants and Measures

The current analyses used self-reported data on depression symptoms, negative life events and maternal punitive discipline collected at Wave 2 of the G1219 study. These were assessed using the short Mood and Feelings Questionnaire (Angold et al, 1995), the total negative event scale of the Life Event Scale for Adolescents (Coddington, 1984) and the Negative Sanctions scale (O'Connor et al, 2001). Of note, negative life events were recorded for their occurrence over the last 6 months prior to data collection.

5.3.2. Statistical Analysis

The various stages of data preparation and analysis of the negative life events and maternal punitive discipline measures followed a similar protocol to that described in Section 4.3.2 with alterations to the *type* of genetic models examined in the present study. As before all descriptive analyses including group differences and phenotypic correlations were conducted using a saturated model in Mx. Model-fitting to raw twin

and sibling data included univariate genetic models incorporating sex effects to examine the presence of genetic influence on each environmental risk measure; bivariate models to investigate the extent to which genetic effects on each environmental risk overlapped with those of depression; and finally, the inclusion of moderation effects within bivariate models to test for the presence of gene-environment interactions whilst controlling for gene-environment correlation. The Wave 2 weight variable as detailed in Section 3.3.1.2 was included in all analyses to account for initial response biases and attrition between Waves 1 and 2. Appendix B.5 to B.6 lists example Mx scripts that have not been discussed in previous Chapters.

5.3.2.1. Descriptive analyses

Saturated models estimating the variance, covariance and means of raw scores were fitted to data for each environmental risk measure. Summary statistics obtained for each sex-specific zygosity group were used to test for mean differences between males and females and between different zygosity groups by comparing various sub-models (see Section 4.3.2.1). Comparability of within-pair covariance among DZ twin pairs and full sibling pairs was also tested using these methods. Age trends in the environmental risk measures, and phenotypic correlations with depression were examined by computing correlation matrices between variables. Descriptive analyses were performed on raw data scores of maternal punitive discipline. The negative life events data was positively skewed, thus a log-transformation [ln(x+1)] was applied to approximate normality.

5.3.2.2. Univariate genetic models

Genetic influences on environmental risk exposure were examined with univariate genetic models, which decompose the variance of each environmental risk measure into genetic (a^2), shared environmental (c^2) and non-shared environmental (e^2) components. A twin similarity effect (t^2) was included if there were significant differences in within-

pair covariance between DZ twin pairs and full sibling pairs. To assess qualitative, quantitative and scalar differences between males and females five different sex-limitation models as detailed in Section 4.3.2.2 were tested and compared.

These models were fitted to age-regressed and where appropriate log-transformed data to minimise any mean effects associated with age and to correct for positive skewness. Each measure was also standardised to reflect deviations from the mean rather than absolute values of risk. To minimise mean differences between sex and zygosity groups, means of these measures were modelled separately for each sex-specific zygosity group in the raw data genetic models. Saturated models estimating summary statistics to describe the means, variance and covariance of one measured variable from each twin/sibling were used for the calculation of fit statistics.

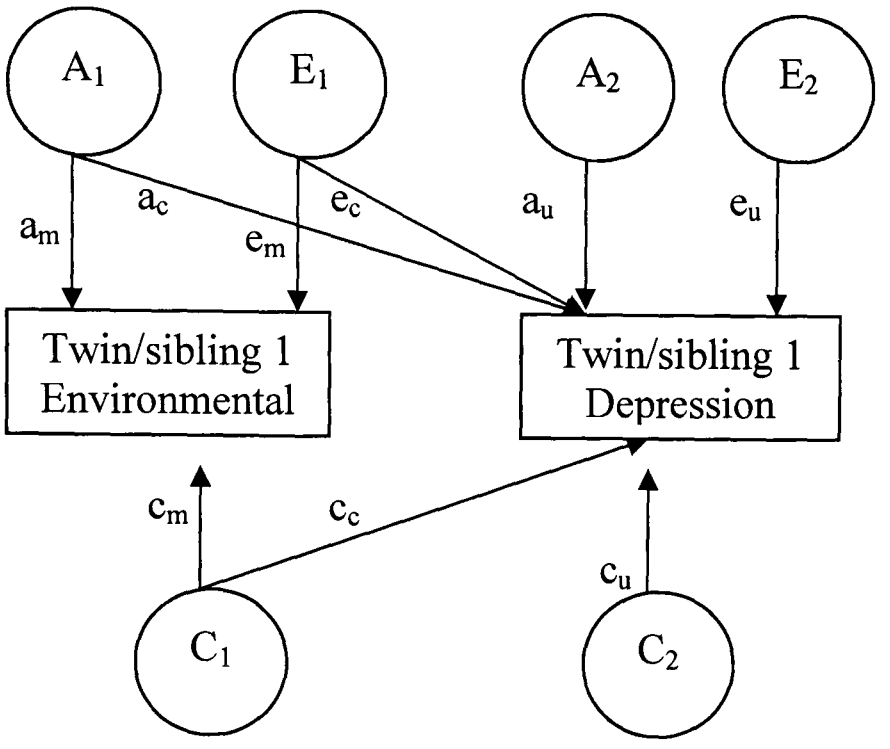
5.3.2.3. Bivariate genetic models

Bivariate genetic models were used to assess the extent of genetic and environmental overlap between each environmental risk measure and depression symptoms. A Cholesky decomposition of two measured variables partitions genetic effects (a^2), shared environmental effects (c^2) and non-shared environmental effects (e^2) into two sets of factor (Figure 5.1). A_1, C_1, E_1 can be thought of as 'common factors' which influence both depression and the environmental risk factor whereas A_2, C_2, E_2 are unique factors to depression. The paths coefficients of the common (a_c, c_c, e_c) and unique effects (a_u, c_u, e_u) on depression and on the environmental risk measure (a_m, c_m, e_m) are estimated from cross-twin/sibling cross-measure covariances (e.g. negative life events of one sibling with depression in the co-sibling) (see Section 4.3.2.3).

As the total genetic variance on depression is composed of common genetic effects (a_c) and unique genetic effects (a_u), the relative proportion by which the common factor explains total genetic variance can be calculated as: $a_c / a_c + a_u$,. This reflects the extent

of overlap in genetic effects between each environmental risk factor and depression. Similarly, $c_c / c_c + c_u$ and $e_c / e_c + e_u$ indicate overlap in shared and non-shared environmental effects respectively between the environmental risk and depression.

Figure 5.1: Bivariate genetic analysis of environmental risk and depression data for one member of a twin/sibling pair



Bivariate genetic models were analysed separately for negative life events and depression symptoms, and maternal punitive discipline and depression symptoms (Appendix B.5). As with univariate analyses, these models were fitted to age-regressed scores, and where appropriate log-transformed. To account for mean differences associated with sex and zygosity, means for all measured variables were modelled separately for each sex-specific zygosity group. Given that there were variance differences between males and females on depression scores, as demonstrated in Section 4.4.2, a sex-specific scalar was included in both bivariate models. Similarly, any sex-specific or twin similarity effects found in univariate models of negative life events and maternal punitive discipline were also incorporated in bivariate models. Saturated models used here for the assessment of model-fit were extended to include estimated summary statistics for two measured variables from each twin or sibling.

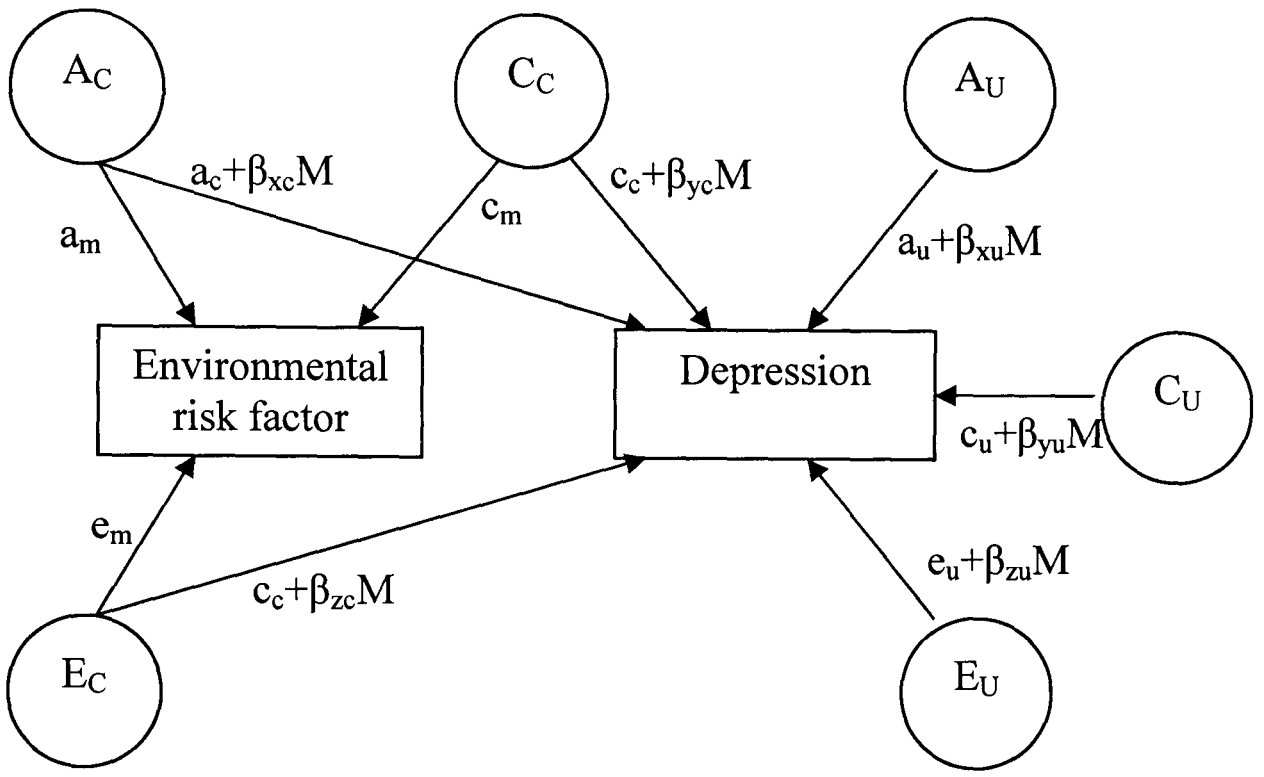
5.3.2.4. Bivariate genetic models including moderation effects

The third stage of analyses involved examining interactions between genetic effects on depression and each environmental risk factor (GxE), whilst simultaneously controlling for the presence of genetic influences on the environmental risk factor (rGE). The environmental moderation of genetic effects on depression, that is, gene-environment interaction, can be incorporated into basic twin and sibling models by re-expressing the genetic path coefficient (a) as a linear function of the environmental risk measure, or the 'moderator' (Purcell, 2002). Thus the genetic path coefficient a, is redefined as $a+\beta_X M$, where a represents a mean (unmoderated) genetic component whilst β_X is the beta coefficient representing potential moderation effect by variable M, the environmental factor. The level of significance of β_X indicates if a linear interaction between the genetic factor and the environmental risk factor is present. Similarly, interactions between shared and non-shared environmental effects on depression with an environmental risk moderator can also be tested, by re-expressing these path coefficients as $c+\beta_Y M$ and $e+\beta_Z M$ and examining the significance of each beta term.

Extending these principles to the paths estimated by the bivariate model of depression and each environmental risk measure allows for simultaneous analysis of gene-environment interactions in the presence of gene-environment correlations. The inclusion of genetic paths which influence both the environmental risk factor and depression in the bivariate model is an assessment of gene-environment correlation, and more specifically, a genetic correlation between the two measures. Thus, by redefining genetic paths on depression as linear functions of the environmental risk factor in this same bivariate model, gene-environment interaction effects can be addressed whilst controlling for gene-environment correlations (Figure 5.2). Furthermore, genetic effects that are involved in both correlation and interaction with the environment can be distinguished by ascertaining the significance of the interaction coefficient associated

with the common genetic factor ($a_c+\beta_{xc}M$) which contributes to both the environmental risk and depression. In comparison, the significance of the interaction coefficient associated with unique genetic factor ($a_u+\beta_{xu}M$) indicates that a different genetic factor is involved in correlation and interaction with the environment.

Figure 5.2: Bivariate model incorporating tests of interaction between environmental risk measure and latent genetic and environmental effects on depression whilst controlling for any genetic correlation between the environmental risk measure and depression for one member of a twin or sibling pair



Following similar principles, interactions between the environmental risk measures and shared and non-shared environmental effects can also be analysed by re-expressing the common and unique factors as linear functions of the environmental risk factor. Any overlap in shared and non-shared environmental variance between the environmental risk measure and depression is taken into account by the 'common' set of factors (C_c and E_c) contributing to both measures. This allows a similar separation of two simultaneous processes: an environment-environment interaction and the sharing of a common environmental risk effect.

Estimating an interaction term between non-shared environmental effects and the environmental risk measure also forms a critical test of the gene-environment interaction model such that the data cannot be explained by heterodasticity (increasing error variance in twins and siblings reporting higher levels of environmental risks). Given that the non-shared environmental term incorporates measurement error, any moderation of this term can assess the effects of heterodasticity. Thus if the genetic interaction is significant after taking into account the moderation of the non-shared environmental factor, it follows that the interaction term cannot be explained just in terms of increased error variance.

The full bivariate model including interaction terms for genetic, shared and non-shared environmental effects on depression symptoms was examined separately for negative life events and maternal punitive discipline (Appendix B.6). The significance of moderation effects were tested by dropping each interaction term from the model whilst assessing changes in χ^2. Non-significant interaction terms were removed to produce the most parsimonious solution. This was then compared with a saturated model to yield measures of overall model-fit. If moderating effects were apparent, the variance components for genetic, shared and non-shared environmental effects on depression were plotted as a function of the environmental risk measure to examine the direction of the interaction effect. Results obtained for negative life events and maternal punitive discipline can offer insight into whether the same environmental risk factors are involved in both correlation and interaction with genetic factors.

These analyses were performed on the same variables as those described in bivariate models. Thus both environmental risk measures were standardised, age-regressed and where appropriate, log-transformed; depression data was age-regressed and corrected by a log-transformation. Any sex-specific or twin similarity effects found in univariate analyses were included in the current model in addition to a sex-scalar effect to account

for variance differences between males and females on depression symptoms. Mx implements moderation effects through definition variables. These are specified to contain the value of the environmental risk moderator for each participant. Thus the saturated model used in calculating fit statistics also included the same number of definition, as well as measured variables as the tested model.

5.4. Results

5.4.1. Descriptive Statistics

Table 5.1 presents means, standard deviations, sample sizes and twin and sibling correlations for negative life events and maternal punitive discipline.

Table 5.1: Data for negative life events and maternal punitive discipline scores at Wave 2 of the G1219 sample in MZ, DZ and FS pairs (SD = standard deviation; N = number of participants; r = correlation)

	MZ twins		**DZ twins**				**Full Siblings**			
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
					Opposite-sex				Opposite-sex	
Negative Life Events										
Mean	1.70	1.70	2.01	1.94	1.92	1.80	1.80	1.91	1.88	2.01
SD	1.82	1.75	1.89	1.82	1.81	1.78	1.67	1.86	1.60	1.81
N[a]	313	387	248	376	323	335	103	184	114	131
r	0.57	0.50	0.42	0.41	0.35		0.03	0.35	0.45	
Maternal Punitive Discipline										
Mean	7.69	7.18	7.12	7.87	7.17	6.97	6.61	6.52	6.24	6.93
SD	4.02	3.82	3.51	3.84	3.70	3.55	3.62	3.71	3.46	3.88
N[a]	289	365	226	353	301	325	96	174	107	129
r	0.55	0.53	0.29	0.38	0.30		0.47	0.40	0.30	

[a] This refers to the number of individuals

Results from testing mean differences between males and females and between zygosity groups, and differences in within-pair covariances between DZ and full siblings using a saturated model are summarised in Table C.4 (Appendix C). There were no significant sex differences on either negative life events (means = 1.83 for females and 1.85 for males) or maternal punitive discipline (means = 14.27 for females and 14.36 for males) as shown by the lack of significant change in fit associated with models, where means are constrained to be equal among males and females. However there were significant differences on both measures which were associated with zygosity type. Further examination of these differences revealed that DZ and full sibling females experienced more negative life events than MZ females, and that for both males and females, full siblings generally reported less maternal punitive discipline.

Finally within-pair covariance among DZ and FS pairs were not comparable on the measure of negative life events. This was driven primarily by the low correlation reported between full sibling male pairs. No significant differences in the within-pair similarity among DZ and FS pairs were shown for maternal punitive discipline. As expected from previous studies (Steinberg & Silk, 2002) age correlated significantly with maternal punitive discipline ($r = -0.16$, $p < 0.001$) with older adolescents reporting less punitive discipline. Age was not significantly correlated with the total number of negative life events reported ($r = 0.01$, n.s.).

5.4.2. Univariate Models of Life Events and Maternal Punitive Discipline

Given a higher DZ relative to FS within-pair covariance, a model including a twin similarity effect was first fitted to the negative life events data. However excluding this term from the model did not result in a significant change in fit: $\Delta\chi^2(1) = 0.02$ (p = n.s.), suggesting that twins are no more alike than siblings in the number of negative events experienced. This parameter was not considered in subsequent analyses.

Sex effects on genetic and environmental parameters of negative life events and maternal punitive discipline were examined by comparing five univariate models, as presented in Table C.5 (Appendix C). As can be seen, for both negative life events and maternal punitive discipline, a model that included no quantitative, qualitative or scalar sex effects provided the best fit to the data. Summary fit statistics with parameter estimates of these no sex-effects models are presented in Table 5.2 for each measure.

Table 5.2: Summary model-fitting statistics of univariate genetic models of negative life events and maternal punitive discipline. Parameter estimates with 95% confidence intervals show proportions of variance due to additive genetic (a^2), shared environmental (c^2) and non-shared environmental (e^2) influences.

	Proportions of variance due to:		
	a^2	**c^2**	**e^2**
Wave 2 Negative Life Events	31 (13-48)	22 (9-34)	47 (41-55)
-2LL = 6276.37, df = 2503, $\chi^2(21) = 18.89$, p = 0.59, AIC = -23.11			
Wave 2 Maternal Punitive Discipline	31 (12-50)	19 (5-33)	50 (43-58)
-2LL = 5904.73, df = 2352, $\chi^2(21) = 13.77$, p = 0.88, AIC = -28.23			

Comparable results were found for each measure. Significant genetic effects on both indicated gene-environment correlation. In addition there were modest but significant shared environmental contributions and large non-shared environmental influences.

5.4.3. Bivariate Models of Environmental Risk Measures and Depression

Phenotypic correlations between depression and each environmental risk measure were significant, at 0.33 ($p < 0.001$) for negative life events and 0.26 ($p < 0.001$) for maternal punitive discipline, indicating that higher levels of both risk factors were associated with more symptoms. To examine the overlap in genetic and environmental variance, bivariate Cholesky decomposition models were tested. Summary fit statistics and parameter estimates are displayed in Table 5.3. The table is divided into effects of

common factors (A_1, C_1, E_1) on the environmental risk measure and depression, and the effects of unique factors (A_2, C_2, E_2) on depression only. Of note the effects of the common factors on depression reflect the degree of genetic and environmental overlap between the environmental risk factor and the phenotype, whilst the effects of the unique factors on depression represent specific variance components.

Table 5.3: Summary model-fitting statistics and parameter estimates with 95% confidence intervals of the bivariate models of depression (DEP) and negative life events (NLE), and depression (DEP) and maternal punitive discipline (MPD).

	Common effects on environmental risk			**Common effects on depression**			**Specific effects on depression**		
	$\mathbf{a^2_M}$	$\mathbf{c^2_M}$	$\mathbf{e^2_M}$	$\mathbf{a^2_C}$	$\mathbf{c^2_C}$	$\mathbf{e^2_C}$	$\mathbf{a^2_U}$	$\mathbf{c^2_U}$	$\mathbf{e^2_U}$
DEP-NLE	29 (11-46)	23 (10-35)	48 (42-56)	8 (1-30)	4 (0-17)	1 (1-3)	28 (5-42)	6 (0-20)	52 (45-59)
-2LL = 12876.98, df = 4991, $\chi^2(70) = 82.49$, p = 0.15, AIC = -57.51, RMSEA = 0.01									
DEP-MPD	32 (13-51)	18 (3-32)	50 (43-58)	10 (1-34)	0 (0-10)	1 (0-3)	26 (1-45)	11 (0-24)	52 (45-59)
-2LL = 12583.12, df = 4840, $\chi^2(70) = 84.79$, p = 0.11, AIC = -55.21, RMSEA = 0.01									

Fit statistics indicate that both bivariate models fit the data well. Genetic and environmental effects on each environmental risk measure mirror closely those obtained from univariate models. A similar pattern of results pertaining to the overlap in genetic and environmental variance with depression symptoms was obtained for negative life events and maternal punitive discipline. In general most of the genetic variation on depression is specific, although both negative life events and maternal punitive discipline share significant genetic variance with depression. For negative life events, this shared genetic effect accounts for 22% of the total genetic variance (8 / 8 + 28) whilst for maternal punitive discipline, this proportion is 28% (10 / 10 + 26). As with results from the univariate genetic models in Section 4.4.2, shared environmental effects

on depression were non-significant, resulting in no significant overlap with either environmental measure. There were significant non-shared environmental effects on depression but these were specific rather than shared with either risk measure.

5.4.4. Bivariate Models of Gene-Environment Interactions and Correlations

Results of testing the significance of each interaction term are summarised in Table 5.4. This table displays the change in model-fit ($\Delta\chi^2$) relative to the change in degrees of freedom (Δdf) associated with excluding a particular interaction coefficient from the full model. Significant departures in fit indicate significant interaction terms.

Table 5.4: Moderation of common and unique genetic and environmental paths by negative life events and maternal punitive discipline

	Moderation by Negative Life Events	**Moderation by Maternal Punitive Discipline**
Genetic effects		
Unique path (β_{XU})	$\Delta\chi^2(1) = 0.01$, p = n.s.	**$\Delta\chi^2(1) = 7.73$, $p < 0.01$**
Common path (β_{XC})	**$\Delta\chi^2(1) = 3.71$, $p < 0.05$**	$\Delta\chi^2(1) = 0.04$, p = n.s.
Shared environmental effects		
Unique path (β_{YU})	$\Delta\chi^2(1) = 0.66$, p = n.s.	$\Delta\chi^2(1) = 0.99$, p = n.s.
Common path (β_{YC})	$\Delta\chi^2(1) = 0.55$, p = n.s.	$\Delta\chi^2(1) = 2.94$, p = 0.09
Non-shared environmental effects		
Unique path (β_{ZU})	$\Delta\chi^2(1) = 0.08$, p = n.s.	**$\Delta\chi^2(1) = 5.62$, $p < 0.05$**
Common path (β_{ZC})	$\Delta\chi^2(1) = 0.91$, p = n.s	**$\Delta\chi^2(1) = 5.12$, $p < 0.05$**

As shown, negative life events significantly moderated common genetic effects on depression. Thus the solution of best-fit to the data included one interaction term, yielding excellent fit statistics when compared with a saturated model: -2LL = 12431.65, df = 4812, $\chi^2(69) = 79.40$, AIC = -58.60, RMSEA = 0.01. Maternal punitive discipline moderated unique genetic effects as well as unique and common non-shared

environmental components on depression. Retaining significant interaction terms in the model also gave excellent fit: -2LL = 11273.58, df = 4316, $\chi^2(67) = 70.91$, AIC = -63.09, RMSEA = 0.01. Figures 5.2 and 5.3 illustrate these significant interactions by showing how variance components change as a function of negative life events and maternal punitive discipline. Total genetic variance increased at higher levels of negative life events and maternal punitive discipline. Total non-shared environmental variance also increased for more severe parental discipline.

Figure 5.3: Plot of genetic variance of depression scores across negative life events

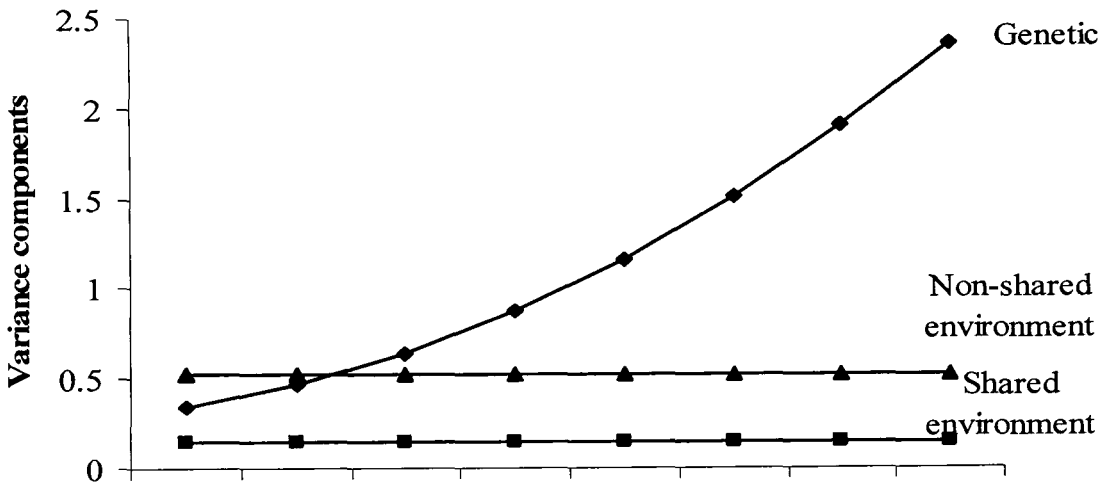
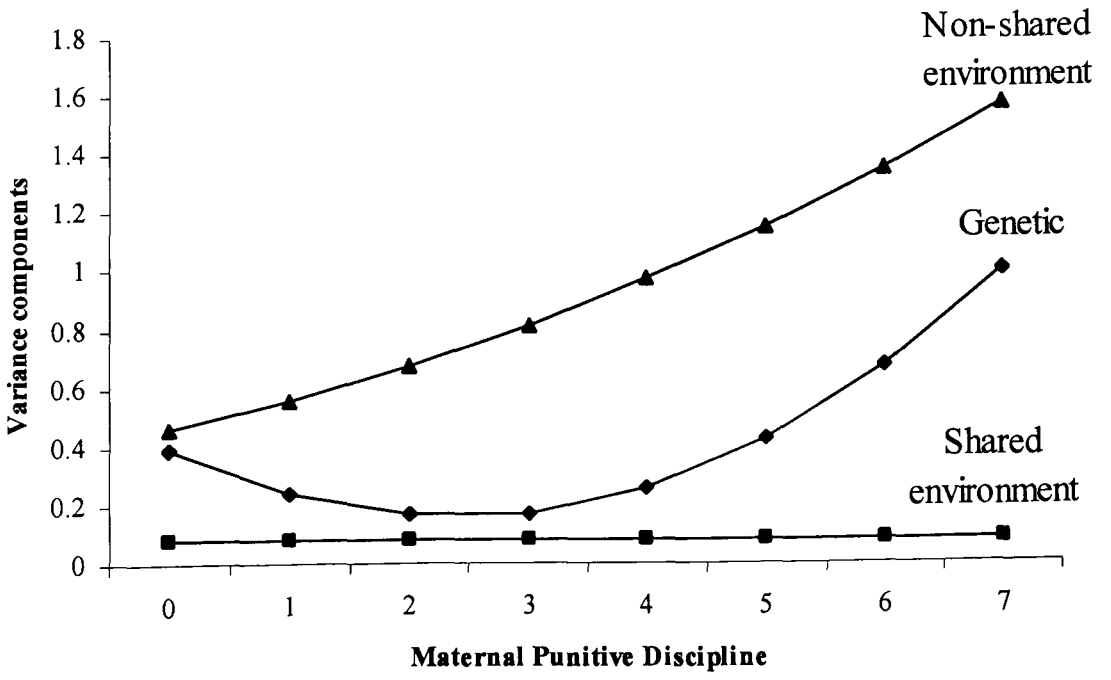


Figure 5.4: Plot of genetic and non-shared environmental variance of depression scores across maternal punitive discipline



5.5. Summary

The present study examined gene-environment correlation and interaction in mid-adolescence. Results show moderate but significant genetic influences on negative life events and maternal punitive discipline, supporting previous claims of gene-environment correlation. More importantly, genetic influences on environmental risk exposure were also involved in depression symptoms, implying that genetic risk for depression may be expressed through risk exposure towards negative life events and negative parental practices. The third set of findings demonstrated that both negative life events and maternal punitive discipline moderated genetic effects on depression, such that genetic variance increases at higher levels of these risks. As these analyses account for confounding effects of gene-environment correlation, this increases the validity of these interactions.

It was apparent that both negative life events and maternal punitive discipline were involved in gene-environment correlations and interactions. However genetic effects which influenced maternal punitive discipline were distinct to those that were subsequently moderated by this risk factor. In contrast the same common genetic factor contributed both towards life events and interacted with this risk factor. Finally, non-shared environmental variance increased across levels of punitive parenting.

These findings highlight a complexity of interplay between genetic and environmental factors on depression, beyond what is typically explored in methodological designs. However several limitations need to be recognised before drawing theoretical and analytical implications. First, all forms of interaction effects are extremely sensitive to scaling variations and may be removed with a change in scale (Rutter & Silberg, 2002). Thus these results need to be replicated in other samples before generalising their effects. This is particularly relevant to results associated with parenting practices, given

that most studies of gene-environment interaction and depression have tended to examine life events. Second, although the current analyses were conducted in a reasonably large sample required for the detection of interaction effects, there were still fewer twin and sibling pairs reporting extreme levels of environmental risks, particularly life events. This means that power to detect genetic effects may decrease at the higher end of the environmental spectrum. However whilst error variance may increase at higher levels of environmental risk (heteroscedasticity), it is reassuring that moderation of genetic paths remained significant, having taken this into account.

A further note on statistical power relates to the distinction between the various interaction coefficients examined. Specifically it is questionable whether there is adequate power to validate the differentiation between interactions involving *unique* genetic effects and those involving *common* genetic components (defined by whether these genetic influences were also involved in gene-environment correlation). A more conservative interpretation of these results would conclude significant gene-environment interactions, rather than the specific genetic sources of this interaction.

A third caveat associated with these results concerns the measurement of each environmental risk measure. Negative life events were assessed by a single indicator which summarised a self-reported 'count' of salient events occurring recently in the individual's life. Whilst it has been argued that such checklists reflect 'objective' measures of life events minimising recall biases, more subjective elements of detailed assessments, such as contextual ratings of severity and personal appraisals are omitted. Moreover, the occurrences of many life events may be inter-related, rather than independent as is assumed by the current measure, where a simple frequency of *all* checked events was totalled. It can also not be discounted that all stressors faced by an individual were adequately captured by the current index. A final possibility to arise when using a summed score of life events to examine similarity among twins (and

siblings) is that many of the events selected may impinge on both individuals (e.g. death of a parent) (Farmer, Harris, Redman, Sadler, Mahmood & McGuffin, 2000). Thus by virtue of being the same event, twin (or sibling) resemblance for life event exposure would be artificially increased, rather than due to genetically mediated risk processes. Parenting was also derived through self-report. The possibility that a negative mood bias, which elicits *perceptions* of parenting rather than *actual* parenting cannot be eliminated. If this were true, any shared genetic effects between this measure of parental discipline and depression symptoms may reflect genetic influences on a negative mood bias or reporting style (Thapar, Harold & McGuffin, 1998), which simultaneously accounts for scores on both these measures, rather than gene-environment correlation. These issues are reminiscent of long-standing debates on the most efficient way of collecting data on psychosocial risk. Future studies may chose to 'budget' for more detailed assessments and corroborate these with other sources, when aiming to assess processes of gene-environment interplay.

A final limitation lies in the cross-sectional design of these analyses, which precludes testing any causal effects between environmental risk variables and depression. Moreover, no assumptions on the time course of gene-environment correlations relative to gene-environment interactions can be made.

In summary the current findings are supportive that genetic risks on depression may be expressed in the exposure towards provoking and chronic stressors, as well as through increased sensitivity towards the occurrence of these psychosocial risks, the implications of which are elaborated in Chapter 8. The present results pave the way for speculating on more intermediate and specific vulnerability factors through which correlations and interactions between genetic and environmental risks are mediated.

Chapter 6: Attributional Style as a Cognitive Risk Factor of Child and Adolescent Depression Symptoms

6.1. Overview

Chapters 4-5 have focussed on examining genetic factors of depression. The current Chapter considers a cognitive explanation of vulnerability to adolescent depression. According to this theory, negative attributions may act as a predisposing factor, emerging during adolescence to account for age-related increases in depression symptoms. Despite the importance of attributional style as a risk factor for depression, its aetiological origins, the nature of its relationship with depression, the causes of developmental changes observed between childhood and adolescence and whether it represents a causal, concurrent or consequential influence of depression remain key questions. Given these issues, the current Chapter set out to examine the genetic and environmental influences on attributional style and whether its association with depression symptoms is reflective of shared genetic and/or shared environmental liabilities. Any developmental changes in these influences were also assessed by extrapolating from cross-sectional comparisons of results obtained in the G1219 and ECHO samples. Finally, a model assessing longitudinal data in the adolescent sample was used to disentangle causal, concurrent and consequential hypotheses between attributional style and depression. Results showed interesting differences in the nature of attributional style in children and adolescents. Attributional style in adolescence was significantly heritable, whereas shared environmental influences were important contributors to attributions in children. Whilst the degree of phenotypic association between attributional style and depression was comparable between adolescence and childhood, shared genetic and environmental factors accounted for roughly equal proportions of this association in adolescence whereas environmental influences were

reflected to a larger degree in childhood. Lastly although attributional style is likely to influence later depression during adolescence, there is also evidence that it co-occurs with symptoms and may even be a 'scar' effect of earlier depression.

6.2. Background

According to the reformulated learned helplessness theory, individuals who make internal, stable and global attributions for negative events and external, unstable and specific attributions for positive events are at-risk for depression. Support for this theory comes from numerous cross-sectional studies and more recently, prospective designs demonstrating significant associations between them (Garber, Keiley, & Martin, 2002). Later elaborations of this theory focussing on the moderating role of negative events on this association have also been reported by some studies (Hankin et al, 2001). Given assertions that this cognitive style emerges in the transition from late childhood to early adolescence following several cognitive maturation factors (Turner & Cole, 1994), the theory can also potentially account for age-related increases observed in depression symptoms during teenage years. Despite the importance of attributional style as a risk factor for adolescent depression, little is known about its aetiological origins, the nature of its relationship with depression or the influences governing age-related changes.

Of the studies to have examined early predictors of attributional style, maternal depression and attributions, and parenting practices have emerged as important 'social' contributors (Alloy et al., 2001; Garber & Flynn, 2001; Murray, Woolgar, Cooper, & Hipwell, 2001). There is little consideration for the alternative yet not mutually exclusive hypothesis that hereditary factors are involved. Whilst there are some indications that genetic factors may influence attributional style, including greater phenotypic similarity reported among monozygotic (MZ) twins compared to dizygotic (DZ) twins (e.g. Schulman et al, 1993), and the findings that parental variables often

involve a combination of genetic as well as environmental risks on child outcomes (Pike et al, 1996), genetic effects on this cognitive factor have yet to be delineated.

However the possibility that genetic as well as environmental effects are important to individual differences in attributional style is intriguing especially for models of depression. Genetic and environmental contributions to depression have been demonstrated consistently in the literature (Section 2.2.2). What is less well-clarified is how these liabilities are expressed. One possibility is that cognitive factors, such as attributional style reflect distal genetic and environmental effects on depression. Negative attributions could constitute a cognitive manifestation of the genetically mediated emotional reactivity or neuroticism that predisposes to depression (Hankin & Abramson, 2001). Similarly attributional style may develop through the incremental effects of negative events, modelling and parenting, thus reflecting a constellation of distal environmental vulnerability on depression. Finally given that life events interact with attributional style to precipitate depression in adolescence, more proximal sources of environmental influence may also be involved in the expression of this relationship.

A key consideration in these speculations on the aetiology of attributional style and its association with depression is developmental context. At a phenotypic level developmental differences in the functioning of attributional style and in its expression of vulnerability to depression have been observed. Attributional style emerges in adolescence following the maturation of several areas of cognition including abstract reasoning and formal operational thought, whereas in childhood, it is thought to be first acquired through the occurrence of negative events and the feedback the child receives regarding the causes and consequences of such events (Turner & Cole, 1994). Attributional style interacts with negative stressors to influence depression during adolescence (Hankin et al, 2001) but may mediate the effects of negative events on depression symptoms in children (Cole & Turner, 1993). Although these changes in the

role of attributional style are likely to reflect a continuous trajectory of development, there may be qualitative differences in its causes at each developmental stage. For example, its emergence in adolescence may be incurred by the expression of several 'developmental' genes that effect neural and in turn, cognitive development, whilst its earlier acquisition may be primarily driven by the child's social environment.

Given that attributional style may reflect the differential impacts of genetic and environmental influences on depression across development, a final question concerning its validity as a predisposing factor on adolescent depression is that of temporal precedence. To date, although there is substantial support for concurrent associations between attributional style and depression (e.g. Gladstone & Kaslow, 1995), demonstrating 'causal' relationships is more problematic, with mixed results. Adding to the complexity is evidence for an 'interlocking' reciprocal relationship between attributional style and depression, such that a negative attributional style is as likely to develop as a consequence of depression as it is to precede it (Garber, Keiley, & Martin, 2002; Nolen-Hoeksema, Girgus, & Seligman, 1992). Systematically disentangling these confounding explanations of attributional style remains a crucial challenge to resolving its role as a vulnerability factor of depression.

The aims of the present Chapter are to address these issues. First genetic and environmental effects on attributional style were examined. Second the contributions of these influences to its association with depression were assessed. Developmental differences in the aetiology of attributional style were inferred by comparing the results obtained in childhood and adolescent samples. Lastly, concurrent, causal and consequential explanations of attributional style were tested. A concurrent aim was to identify sex differences in the patterns of aetiological influences on attributional style and its association with depression during adolescence. Given marked differences

between males and females in depression rates in this age range, sex effects in the aetiology of vulnerability factors, such as attributional style may be a driving force.

6.3. Methods

6.3.1. Participants and Measures

The current analyses used self-reported data on attributional style and depression symptoms collected from Wave 1 of the ECHO child sample and Waves 2 and 3 of the G1219 adolescent sample. Attributional style was assessed in both samples using the Children's Attributional Style Questionnaire (Kaslow & Nolan-Hoeksema, 1991). Lower scores on this scale indicate a more negative attributional style. Depression symptoms were reported using the Children's Depression Inventory (Kovacs, 1981) in the ECHO child sample, and the short Mood and Feelings Questionnaire (Angold et al, 1995) in the G1219 adolescent sample. Of note, a four-point scale was used at Wave 2 of G1219 whilst a three-point scale was used at Wave 3 (see Section 3.3.1).

6.3.2. Statistical Analysis

The various stages of data preparation and analysis of the attributional style and depression symptoms measures followed a similar protocol to that described in Section 4.3.2 with alterations to the type of genetic models examined in the present study. All descriptive analyses including group differences analyses and phenotypic correlations were conducted using a saturated model specified in Mx. Model-fitting to raw twin (and sibling) data included univariate genetic models incorporating sex-effects to identify genetic and environmental influences on attributional style; bivariate models to examine the extent to which shared genetic and environmental factors accounted for the concurrent association between attributional style and depression; and finally reciprocal causation modelling on longitudinal data to systematically assess competing hypotheses

of concurrent, causal and consequential effects between attributional style and depression symptoms in adolescence.

As with analyses conducted in Chapter 4, different analytic techniques sensitive to the nature of each sample's study design were used. Most notably weighting variables which account for any initial response bias and subsequent attrition were included (see Section 3.3.1.2), whilst for all ECHO analyses, the selection variable is included to correct for the selected nature of the sample (see Section 3.3.2.2). Appendix B.7 to B.8 lists example Mx scripts used here that have not been discussed in previous Chapters.

6.3.2.1. Descriptive analyses

Saturated models which estimate the variance, covariance and means of raw scores were fitted to attributional style data collected at Waves 2 and 3 of the G1219 sample and Wave 1 of the ECHO sample. Summary statistics obtained for each sex-specific zygosity group were used to test for mean differences between males and females and between different zygosity groups by comparing various sub-models (see Section 4.3.2). In addition comparability of within-pair covariance among DZ twin pairs and full sibling pairs was also tested using these methods. Age trends in the environmental risk data, and phenotypic correlations between attributional style and depression were examined in Mx by computing correlation matrices between these variables. Descriptive analyses were performed on raw scores of attributional style.

6.3.2.2. Univariate genetic models

Genetic and environmental influences on attributional style were identified by univariate genetic models, which decompose the variance of these measures into genetic (a^2), shared environmental (c^2) and non-shared environmental (e^2) effects. A twin similarity effect (t^2) was included if there were significant differences in within-pair

covariance between DZ twin pairs and full sibling pairs. Univariate genetic models incorporating qualitative, quantitative and scalar differences between males and females were examined for attributional style data collected from the G1219 adolescent sample. This involved a comparison between five different sex-limitation models (see Section 4.3.2.2) in terms of fit statistics. Due to the smaller sample size of the ECHO study, and therefore less power to detect sex differences, the various sex-limitation models were not considered for these data. Instead a single set of results equated across males and females were presented for the univariate genetic model and subsequent tested models.

These models were fitted to age-regressed scores to minimise any mean effects associated with age. To control for mean differences between sex and zygosity groups, means of each measure was modelled separately for each sex-specific zygosity group in the raw data genetic model. Saturated models estimating summary statistics to describe the means, variance and covariance of one measured variable from each twin/sibling were used for the calculation of fit statistics.

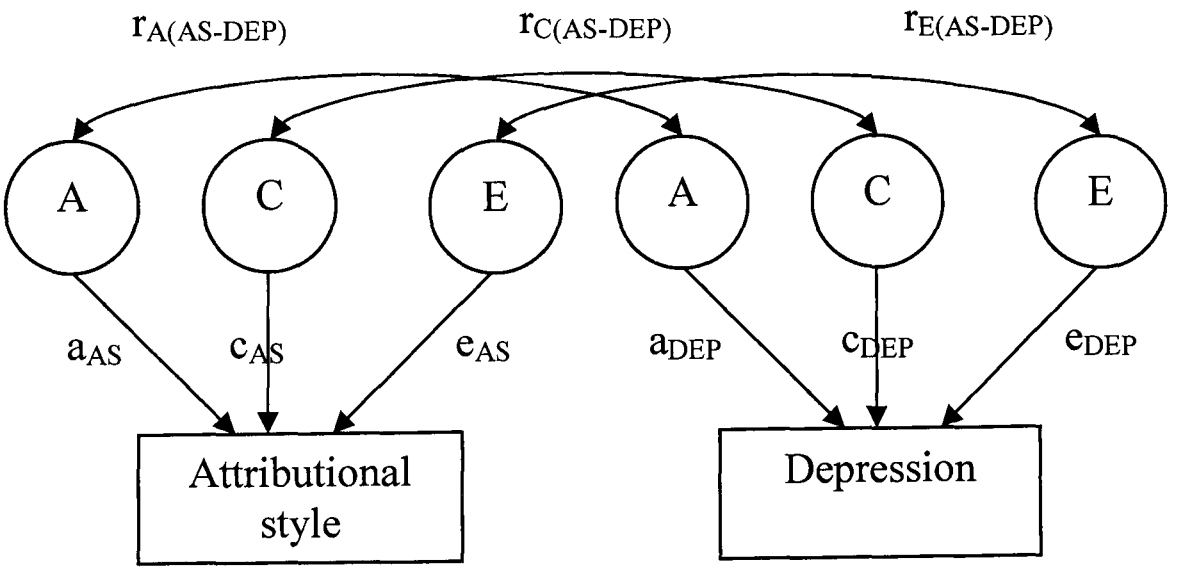
6.3.2.3. Bivariate genetic models

Bivariate models were utilised to examine whether attributional style and depression share the same genetic and environmental liabilities, and the extent to which these account for their association. As described in Section 5.3.2.3, a Cholesky decomposition of two measured variables partitions genetic (a^2), shared environmental (c^2) and non-shared environmental effects (e^2) into 'common' and 'unique' sets of factors. The paths coefficients associated with these two sets of factor are estimated from cross-twin/sibling cross-measure covariances (e.g. attributional style of one sibling with depression in the co-sibling). The ordering of variables in a Cholesky decomposition is an a priori consideration, justified typically by the time sequence of the data (e.g. longitudinal depression data, Chapter 4) or theoretical grounds for assigning one

variable before another (e.g. environmental risk effects on depression, Chapter 5). However the current model was performed on measures of attributional style and depression symptoms collected in the same time-frame, with inadequate evidence for a temporal relationship. Thus a non-directional transformation of the Cholesky model, the correlated factors solution was reported.

This solution, represented pictorially in Figure 6.1, offers a different interpretation of the data to the Cholesky decomposition. Similar to univariate models, each path on a variable represents the (unsquared) estimates of heritability, shared environmental and non-shared environmental effects of that variable. The correlational paths between the latent factors are the genetic (r_A) shared (r_C) and non-shared (r_E) environmental correlations, which correspond to the strength of the association between genetic, shared and non-shared environmental influences on each variable. Thus the higher the correlation, the more likely the influences on two measures are identical.

Figure 6.1: Correlated Factors Solution of the Cholesky Decomposition bivariate model for one member of a twin or sibling pair



The extent to which these shared genetic, shared and non-shared environmental factors contribute to the phenotypic correlation between variables can also be obtained. For example, genetic contributions to the correlation are calculated as the product of the

genetic paths on each variable (a_{AS} and a_{DEP}, which are the square root of their respective heritabilities) and the genetic correlation ($r_{A(AS\text{-}DEP)}$). Similar calculations for shared and non-shared environmental paths (C_{AS} and C_{DEP}, E_{AS} and E_{DEP}) and shared and non-shared environmental correlations ($r_{C(AS\text{-}DEP)}$ and $r_{E(AS\text{-}DEP)}$) yield shared and non-shared environmental contributions on the correlation. To re-express each of these as proportions of the correlation, they are divided by the overall phenotypic correlation.

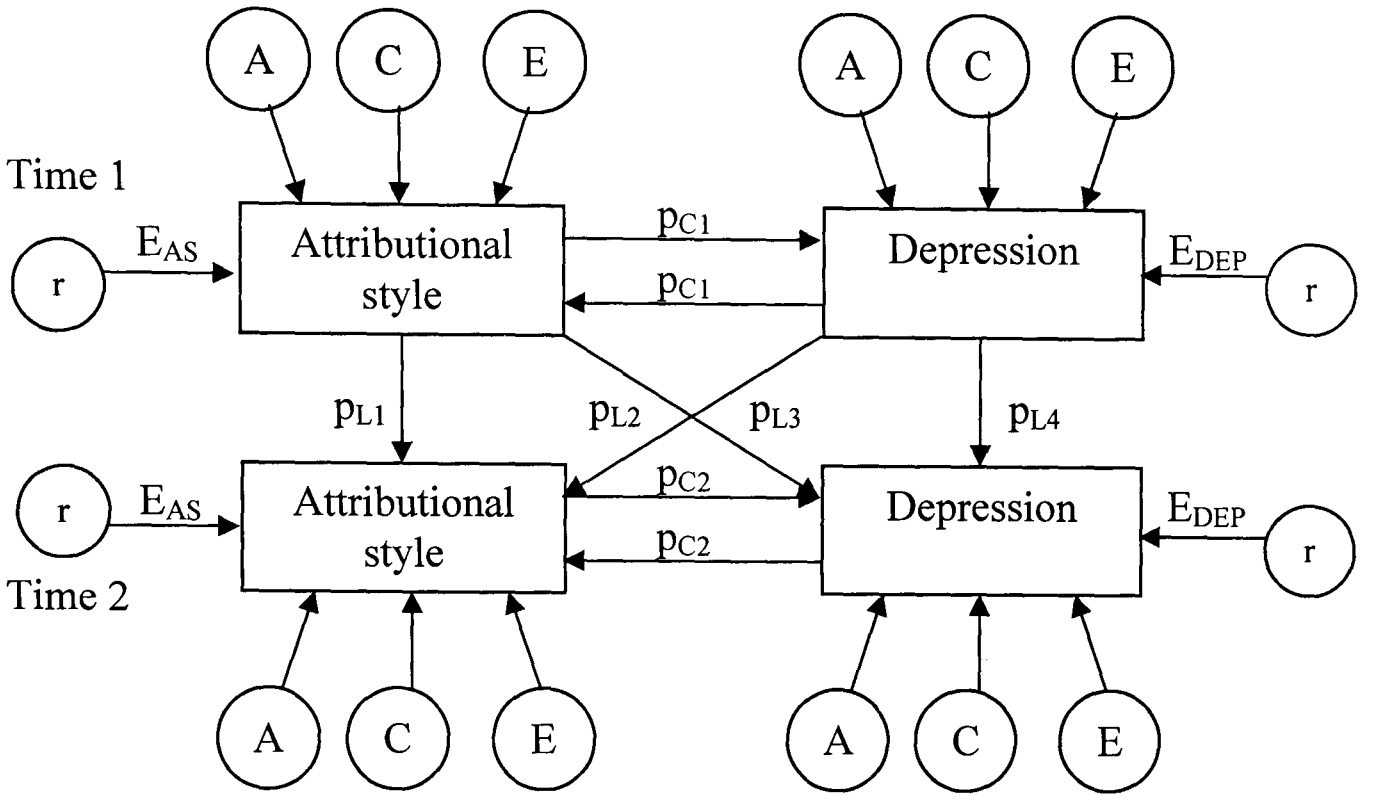
This transformed solution of the Cholesky decomposition, the correlated factors model was reported for measures of attributional style and depressive symptoms at Waves 2 and 3 of the G1219 sample and Wave 1 of the ECHO sample (Appendix B.7). As with univariate analyses, these models were fitted to age-regressed scores of attributional style and depression symptoms. Given the positive skew of the depression distributions at Waves 2 and 3 of the G1219 study, these measures were log-transformed (Section 4.3.2). To account for mean differences associated with sex and zygosity, means for all measured variables were modelled separately for each sex-specific zygosity group. As there were variance differences between males and females on depression scores at Wave 2 of the G1219 data (Section 4.4.2), a sex-specific scalar was included in these bivariate models. Any sex-specific or twin similarity effects found in univariate models of adolescent attributional style were also incorporated. Saturated models used here for the assessment of model-fit were extended to include data from two measured variables for each twin or sibling.

6.3.2.4. Reciprocal Causation Model

The final set of analyses focussed on testing a cross-lagged phenotypic causal model using longitudinal data collected on attributional style and depression symptoms in the G1219 adolescent sample. This model utilises the covariance among measures to

estimate direct causal paths (Figure 6.2) rather than deriving the effects of shared variance components typically assessed in a standard multivariate genetic model.

Figure 6.2: Full direct phenotypic contribution model of attributional style and depression data at Waves 2 and 3 for one member of a twin or sibling pair



In this model estimating longitudinal contributions within and across measures (p_{L1}, p_{L2}, p_{L3}, p_{L4}) is reliant on the asymmetry that is present in cross-time, cross-measure correlations. That is, the correlation between attributional style at Time 1 and depression symptoms at Time 2 is not identical to the correlation between depression symptoms at Time 1 and attributional style at Time 2, allowing for relative cross-time contributions from one measure to the other to be assessed. A similar idea can be applied to cross-sectional data from pairs of relatives to ascertain the *direction* of causal effects between measures collected in the same time-frame (p_{C1}, p_{C2}) (Neale et al., 1994) but the power to distinguish between two paths, for example, attributional style causing depression versus depression causing attributional style, is greatest when the two measured variables have very different modes of inheritance (Heath et al., 1993). As attributional style and depression in the current adolescent sample showed very similar profiles of genetic and environmental effects as ascertained in univariate and bivariate analyses, the

direction of causation within the same time-frame could not be inferred in the current analyses. Instead causal paths within time (p_{C1}, p_{C2}) were constrained to be the same and interpreted as correlational concurrent effects.

Thus a model containing six paths representing the associations between attributional style and depression within and across time-points were examined (Figure 6.2). The significance of each path was tested by dropping the appropriate parameter from the model whilst assessing changes in model-fit. Non-significant paths were dropped from the model to produce a more parsimonious solution. Of note, whereas p_{L1} and p_{L4} are reflective of the stability of attributional style and depression respectively across time, p_{L2} and p_{L3} facilitate causal and consequential interpretations respectively. In comparison p_{C1} and p_{C2} signify the presence of concurrent effects across measures within the same time-frame but make no assumptions regarding the direction of causation. In addition to assessing these paths, two separate measurement error parameters (E_{AS} and E_{DEP}) were specified in the model for each measure given that such models may be particularly sensitive to measurement error. This is made possible by having data from two different occasions. The contribution of measurement error is constrained to be the same for each measure across time-points.

To test for the identification of the model (i.e. that there are enough observed statistics to estimate the number of parameters), data were first generated with a set of fixed values for the parameter estimates. Next, estimation of these model parameters using this dataset but with a different set of starting values was conducted. In the case of an identified model, this optimisation procedure should recover a set of parameter estimates that are equivalent to the original set of values used to generate the data (Neale et al, 1999). This empirical test showed that the current model was identified.

As before, these analyses were performed on depression symptoms and attributional style collected at Waves 2 and 3 (Appendix B.8). As before age effects were regressed from all measures. Positive skewness of the depression measures were corrected by a log-transformation. Sex-specific or twin similarity effects from univariate models of attributional style, in addition to a scalar effect for the depression data at Wave 2 were incorporated into the current model. Model-fit of the final model which included only significant paths, was compared with a saturated model, which estimated the means, variance and covariance of four measured variables from each twin or sibling.

6.4. Results

6.4.1. Descriptive Statistics

Table 6.1 presents means, standard deviations, sample sizes and correlations of twin and sibling pairs across males and females for attributional style in ECHO and G1219. Results from testing mean differences between males and females and between zygosity groups, and differences in within-pair covariances between DZ and full siblings using a saturated model in the two samples are summarised in Table C.6 (Appendix C). Significant sex differences in mean attributional style scores emerged at at Wave 1 of the ECHO study (mean = 5.01 for females and 4.14 for males) and Wave 2 of the G1219 study (mean = 4.50 for females and 4.18 for males) but not at Wave 3 (mean = 4.32 for females and 4.50 for males). Contrary to expectations, males reported more negative attributions.

There were also significant zygosity differences at Wave 2 of the G1219 study, and further examination of this result indicated that MZ females reported more positive attributional styles compared with DZ and full sibling females. Finally, comparison of sub-models showed no significant differences in the within-pair covariance between DZ

twins and full siblings. Phenotypic correlations with age at Waves 2 and 3 of the G1219 study were small, at r = 0.02 (p = ns) for Wave 2 and r = -0.05, (p < 0.05) for Wave 3.

Table 6.1: Descriptive data on attributional style at Wave 1 of ECHO and Waves 2 and 3 of the G1219 sample by sex-specific zygosity groups (SD = standard deviation; n = number of participants; r = correlation).

	MZ twins		**DZ twins**				**Full Siblings**			
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
					Opposite-sex				Opposite-sex	
ECHO Wave 1 Attributional style: 8 years (mean = 8 years 6 months)										
Mean	4.20	5.01	3.82	4.53	4.55	5.46				
SD	3.38	2.64	2.87	3.05	3.29	2.81				
N[a]	76	106	51	97	101	104				
r	0.24		0.26							
G1219 Wave 2 Attributional style: 12-21 years (mean = 15 years)										
Mean	4.32	4.90	4.25	4.28	3.98	4.52	3.82	4.15	4.22	4.30
SD	3.27	3.12	3.31	3.20	3.40	3.20	3.20	3.35	3.21	3.56
N[a]	300	377	242	365	307	329	105	180	111	129
r	0.29	0.45	0.29	0.31	0.20		0.13	0.28	0.18	
G1219 Wave 3 Attributional style: 14-23 years (mean = 17 years 8 months)										
Mean	4.61	4.45	4.37	4.35	4.24	4.19	4.39	4.25	5.20	4.00
SD	3.36	3.58	3.12	3.69	3.36	3.63	3.23	3.54	3.31	3.94
N[a]	175	264	125	260	193	218	47	97	60	80
r	0.32	0.51	0.21	0.24	0.26		0.15	0.19	0.28	

6.4.2. Univariate Models of Attributional Style

Sex effects on genetic and environmental parameters of attributional style in the G1219 adolescent sample were examined by comparing five univariate models. Fit statistics comparing these models are presented in Table C.7. (Appendix C). As can be seen, there were no qualitative or quantitative sex differences in genetic and environmental

parameters influencing attributional style at Waves 2 or 3. However a model including variance differences between males and females provided the best fit to Wave 3 attributional style. Due to less power available for the detection of sex effects in the ECHO sample, no sex-effects were examined. As such a single set of parameters for males and females was estimated for both samples as presented in Table 6.2 with summary fit statistics.

Table 6.2: Model-fitting statistics from univariate genetic models of attributional style in childhood and adolescence. Parameter estimates with 95% confidence intervals show proportions of variance due to a^2 (additive genetic influences), c^2 (shared environmental influences), e^2 (non-shared environmental influences).

	Proportions of variance due to:		
	a^2	**c^2**	**e^2**
ECHO: Wave 1 Attributional style	8 (0-43)	18 (0-34)	74 (57-88)
-2LL = 29262.83, df = 10925, $\chi^2(38) = 45.23$, p = 0.20, AIC = -30.77, RMSEA = 0.03			
G1219: Wave 2 Attributional style	31 (12-50)	19 (5-33)	50 (43-58)
-2LL = 6151.99, df = 2429, $\chi^2(21) = 19.08$, p = 0.58, AIC = -22.92			
G1219: Wave 3 Attributional style	38 (10-53)	5 (0-25)	57 (47-69)
-2LL = 3261.47, df = 1481, $\chi^2(20) = 12.20$, p = 0.91, AIC = -27.80			

Results are presented in order of the age of when data were collected across samples so as to facilitate cross-sectional comparisons of parameter estimates. This revealed a general pattern of increasing genetic effects from childhood to adolescence. Whilst significant genetic influences emerged at both time-points in the adolescent sample accounting for approximately 30% of the variance, these were small and non-significant in childhood, as indicated by confidence intervals which overlapped with zero. Conclusions regarding shared environmental effects were more speculative. Although confidence intervals of this parameter overlap with zero in childhood, excluding both this and the genetic parameter from the model, resulted in a significant deterioration in

fit. This implicates familial factors but the power to distinguish between genetic and shared environmental effects was limited ($\Delta\chi^2(4) = 16.81$, $p < 0.05$). However given that the effect size of the shared environmental component was larger than that of the genetic parameter, it is likely that this source of influence is relevant. If this were the case, the results point to a pattern of effects whereby shared environmental influences are more important to childhood attributional style than they are in adolescence. Finally, non-shared environmental effects were consistently substantial at all three age periods.

6.4.3. Bivariate Models of Attributional Style and Depression

Phenotypic correlations between attributional style and depression were -0.48, -0.39 and -0.45 for the ECHO child sample, and Waves 2 and 3 of the G1219 adolescent sample respectively. To examine whether these correlations are due to shared genetic and/or environmental liabilities, a transformation of the Cholesky decomposition, the correlated factors solution was reported. This gives two types of information. The first are the genetic, shared and non-shared environmental correlations, which refer to the strength of the association in genetic, shared and non-shared environmental influences on each measure. The second is the degree to which these shared factors account for the phenotypic correlation between the two measures. Results from this bivariate model are displayed in Table 6.3 for ECHO Wave 1 and G1219 Waves 2 and 3 data.

Although all three models showed good fit to the data, confidence intervals on all parameters are wide, particularly those from ECHO analyses, due partly to the lower power associated with the small sample size. As such, most parameter estimates are not significant given that the confidence intervals overlap with zero. Of note, if genetic, shared and non-shared environmental correlations are not significant, the proportions by which these shared effects account for the phenotypic correlation will also not be significant, given that the latter are derived from the former estimates. This increases

the difficulty of drawing firm conclusions of many of these estimates, and interpretations of the table are based mainly upon effect sizes of parameters.

Table 6.3: Model-fitting statistics and parameter estimates with 95% confidence intervals of the bivariate models of attributional style in childhood and adolescence. r_A, r_C and r_E represent genetic, shared environmental and non-shared environmental correlations respectively. a^2, c^2 and e^2 are the proportions of phenotypic covariance due to genetic, shared environmental and non-shared environmental influences.

	Genetic, shared and non-shared environmental correlations with 95% CI			**Proportions of correlation with 95% CI:**		
	r_A	r_C	r_E	a^2	c^2	e^2
ECHO W1	-0.06 (-1.00 to 1.00)	-0.99 (-1.00 to 1.00)	-0.36 (-0.48 to -0.19)	1 (0-66)	42 (0-63)	57 (29-79)
-2LL = 30738.08, df = 11482, $\chi^2(87)$= 95.06, p=0.26, AIC = -78.94, RMSEA = 0.02						
G1219 W2	-0.37 (-0.78 to 0.12)	-0.89 (-1.00 to 1.00)	-0.29 (-0.38 to -0.20)	31 (0-69)	25 (0-51)	44 (29-60)
-2LL =12646.87, df = 4917, $\chi^2(70)$ = 88.62, p=0.07, AIC = -51.38, RMSEA = 0.01						
G1219 W3	-0.72 (-1.00 to -0.43)	-1.00 (-1.00 to 1.00)	-0.27 (-0.38 to -0.15)	66 (27-90)	1 (0-28)	34 (19-50)
-2LL = 7163.36, df = 3021, $\chi^2(70)$ = 78.69, p=0.22, AIC = -61.31, RMSEA = 0.01						

The most apparent trend is the increase in genetic overlap across age, as shown by stronger genetic correlations estimated in the Wave 3 G1219 data compared to Wave 2 of G1219 and Wave 1 of ECHO data. This indicates that by late adolescence, attributional style and depression share more genetic risks compared to earlier periods. Conclusions on shared environmental correlations are more limited given that these are estimated as non-significant across all time-points. In the G1219 measures, this may be due to the lack of significant shared environmental effects demonstrated on both attributional style and depression in the univariate analyses. In ECHO analyses neither

genetic nor shared environmental correlations between variables were significant, driven primarily by the non-significant genetic and shared environmental influences on each measure. Thus the extent to which depression and attributional style share familial factors cannot be delineated in the current study. In comparison, non-shared environmental correlations between attributional style and depression were moderate across all three time-points suggesting some specificity in non-shared environmental influences on these measures.

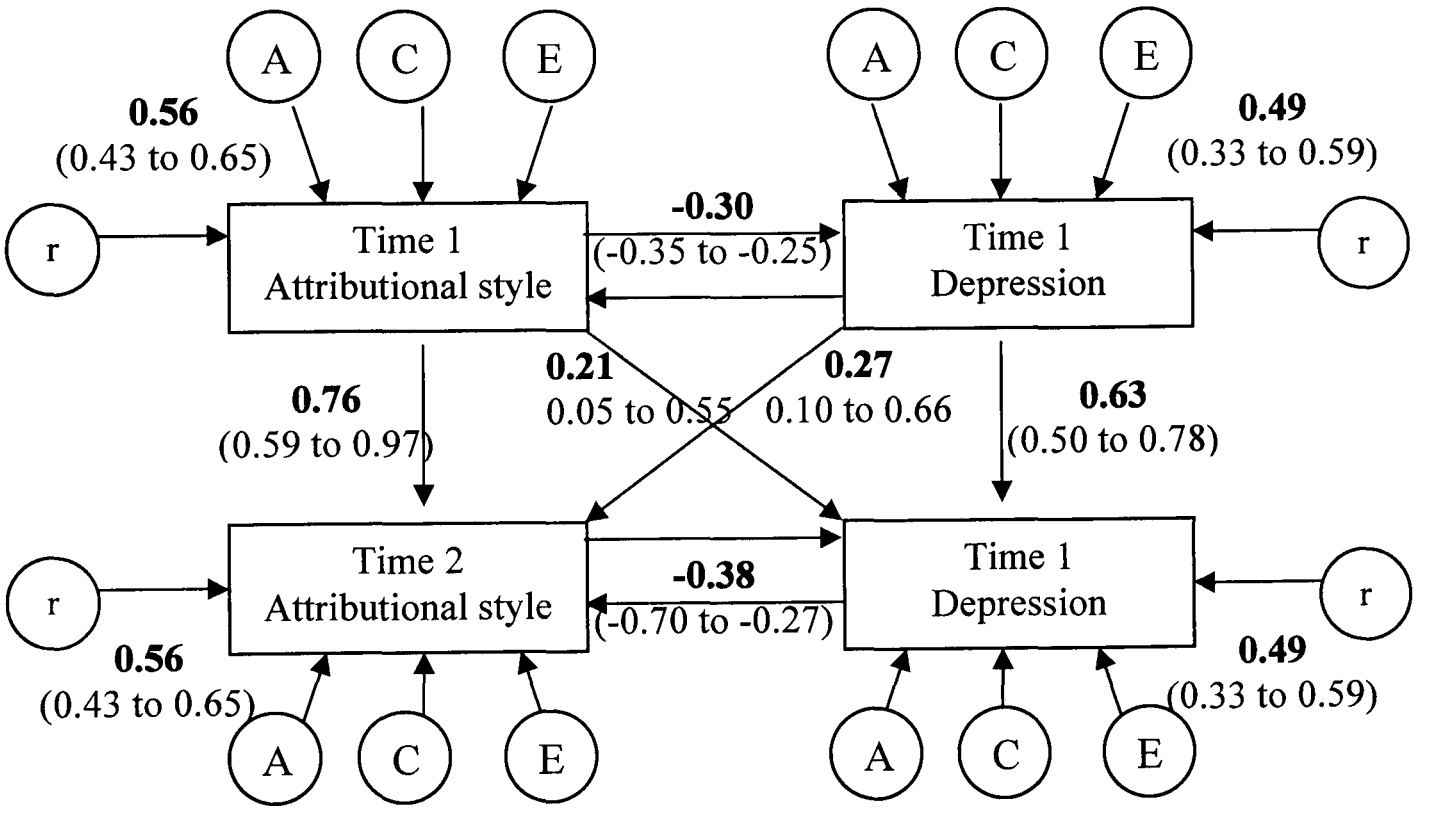
The second type of information relates to the extent to which these shared genetic and environmental effects contribute towards the phenotypic correlation between attributional style and depression. As demonstrated, phenotypic correlations at all three time-points were comparable: -0.48, -0.39 and -0.45 for Wave 1 ECHO, Wave 2 G1219 and Wave 3 G1219 respectively. However the degree to which shared genetic and environmental effects accounted for these associations was quite different at each time-point. In the ECHO data, the relative effect sizes indicate that if common shared environmental effects were significant, these may account for the relationship between attributional style and depression. For both Waves of data in the G1219 sample, common genetic effects may be more important influences on this association. Common non-shared environmental contributions were apparent at all three time-points.

6.4.4. Cross-Lagged Phenotypic causal model

The final set of analyses examined directional paths between attributional style and depression measures within time and across time in the adolescent sample. The full model contained 6 paths, which accounted for the covariance between attributional style and depression measures, and 2 paths representing measurement error. Of the 6 paths between measures of attributional style and depression, these included 4 paths representing directional effects between measures of attributional style and depression

across time and 2 paths reflecting concurrent effects. Testing the significance of each path involved the removal of this path coefficient, and assessing the change in model-fit relative to the full model. These results are presented in Table C.8 (Appendix C). As can be seen, all 8 paths were significant, and these parameter estimates with 95% confidence intervals are displayed in Figure 6.3. Thus the full model fit the data best, and showed excellent overall fit statistics, as compared with a saturated model: -2LL = 15586.90, df = 6458, $\chi^2(276) = 359.51$, p = 0.001, AIC = -192.49, RMSEA = 0.02.

Figure 6.3: Full direct phenotypic contribution model of Waves 2 and 3 attributional style and depression measures. A, C and E are the variance components for each path and R is the measurement error. Significant parameter estimates representing phenotypic paths are presented with 95% confidence intervals.



The parameter estimates of directional paths between attributional style and depression can be interpreted as regression coefficients free from measurement error. Significant concurrent effects were demonstrated between depression and attributional style at both time-points although the direction of causation between these measures could not be

ascertained. Both measures showed high stability across time. Attributional style predicted later depression but was also influenced by earlier symptoms of depression.

6.5. Summary

The present Chapter addressed several issues relating to the role of attributional style as a vulnerability factor for depression. Results in the adolescent sample demonstrate moderate but significant genetic influences on individual differences in attributional style with the remaining variance accounted for by non-shared environmental effects. Shared environmental influences in this age range, by comparison were small and non-significant. A large overlap in genetic variance between attributional style and depression, which becomes stronger from mid to late-adolescence, was also found. Furthermore this shared genetic liability was instrumental in accounting for their phenotypic correlation, particularly at the later time-point in adolescence.

Considering these parameter estimates in a developmental context to better understand the trajectory of attributional style reveals a different profile of effects between the child and adolescent samples. Mimicking the pattern found in depression symptoms, genetic effects were small and non-significant in childhood, Shared environmental influences on attributional style were also non-significant, but the effect size of this parameter was considerably larger. Excluding both parameters resulted in a significant decrease in fit, which suggests that familial factors are important in the development of this aspect of cognition. Non-shared environmental effects were also substantial in accounting for attributional style in this age range. Bivariate analyses indicated only a significant overlap in non-shared environmental factors between attributional style and depression. Conclusions on whether these measures also share familial factors were fairly limited due to wide confidence intervals around the parameters, indicating non-significance.

The final set of analyses provided evidence for attributional style as a concurrent, causal and consequential effect of depression. Although the current design lacked the power to distinguish between the direction of causation between attributional style and depression collected at a single time-point, concurrent correlations were of a size consistent with previous studies. Support for a causal role, such that attributional style at an earlier time-point preceded depression was also found. Interestingly these negative cognitions were likely to reflect the effects of depression symptoms reported at an earlier time-point too. Thus these findings are in line with an interlocking reciprocal relationship between attributional style and depression.

There are several limitations associated with the interpretation of these findings that need to be made explicit. Similar to previous analyses, the results of univariate and bivariate models using the ECHO child sample should be considered cautiously, given the wide confidence intervals that overlapped with zero on many of the parameter estimates. Thus conclusions concerning the role of genetic and shared environmental factors on attributional style in childhood and developmental comparisons made with adolescents should be regarded preliminary rather than definitive.

The second limitation concerns the reliability and validity of the measure of attributional style. The Children's Attributional Style Questionnaire is a well-known but psychometrically poor measure with often low internal consistency. In the current samples, these were 0.61 and 0.66 in the adolescent sample, and 0.55 for the child sample. In addition to issues of reliability which may be due to the dichotomous nature of the measure, studies have also questioned the validity of its sub-scales and more importantly, the concept of attributional style. That is, the notion of whether children and adolescents possess a consistent explanatory 'style' which applies across all positive *and* negative situations. These doubts have been driven in part by weak support for the proposed factor structure which underlies the scoring of this questionnaire (e.g.

(Cunningham, 2003). More specifically, factor analyses very often do not converge on meaningful factors, let alone the unidimensional sub-scales (internal, global and stable), which lie at the centre of the theory. One possible reason for this is that explanatory styles have been found to differ across domains, thus the types of attributions used are dependent on specific situations, for example interpersonal versus academic (Turner & Cole, 1994). Instead of one universal attributional style, there may be domain-specific styles. In light of all these complexities, the current study may have been reliant on an overly simplistic index of this cognitive factor, calculated on the basis of difference scores between pessimistic attributional styles for negative events and optimistic attributional styles for positive events. Nevertheless, reasonable across-time reliability (stability) of this measure was demonstrated, in addition to moderately sized associations with depression symptoms in both samples. However the validity of the current results are dependent on replications using more reliable and valid measures of attributional style (e.g. Hankin & Abramson, 2002) before firm conclusions on its role as a vulnerability factor on depression are drawn.

A final source of scepticism directed specifically towards the last set of results is the legitimacy of drawing conclusions of causality on the basis of temporal precedence between variables. Interpretations of the current results have focussed on concurrent and reciprocally causal relationships between attributional style and depression symptoms. However an alternative explanation is that attributional style is a measure of a person's characteristic level of distress over a protracted period of time, a concomitant or state feature of the depressed phenotype. This argument has also been applied to neuroticism (Farmer et al, 2002) and dysfunctional attitudes (e.g. Farmer, Harris, Redman, Mahmood, Sadler & McGuffin, 2001), other measures which have also been proposed as candidates of familial vulnerability on depressive symptoms. Specifically these authors make the suggestion that prospective associations between these measures and

depressive outcomes are circular and tautological (Ormel, Rosmalen & Farmer, 2004), and furthermore that until the psychobiological mechanisms underlying the vulnerability associated with neuroticism are clarified, the explanatory power of these factors in predisposing a psychopathological outcome is lessened. In light of this equally feasible interpretation of the data on attributional style, care should be taken in inferring causality from longitudinal data alone.

In summary, the current findings have provided some support that attributional style and depression may be manifestations of the same genetic liability during adolescence. This relationship is not static but instead changes dynamically with development. The role of attributional style as a predisposing factor on depression is difficult to pinpoint, given that it precedes, co-occurs and follows depression symptoms. Moreover, true relations of cause and effect are difficult to demonstrate among psychological constructs. The implications of these results are fully elaborated in Chapter 8. In the next Chapter, the role of attributional style and its shared genetic liability with depression will be further contextualised within psychosocial explanations of this phenotype.

Chapter 7: Psychosocial Risk Mechanisms of Child and Adolescent Depression Symptoms

7.1. Overview

Findings from multiple research disciplines have indicated that depression is a multifactorial phenotype, a developmental product of the combined effects of several domains of putative risk factors. Environmental influences form one important domain in addition to genetic and cognitive factors, which were considered in detail in previous Chapters. Although the preceding Chapters have already alluded to the importance of the environment, it has typically been defined as the remainder variance in depression symptoms, unaccounted for by genetic influences, and with exception to Chapter 5, there have been limited attempts across the present studies to identify specific aspects of the social environment that contribute towards depressive symptomatology. Thus the first aim of this Chapter was to consider several candidates of psychosocial risk and more specifically, the risk mechanisms by which these effects are exerted. A second goal was to examine the role of attributional style as a cognitive mediator of psychosocial risk and as a moderator of negative life events. These pathways were explored in the context of previously demonstrated genetic risk mechanisms on depressive outcome. Using path analysis, a multidomain causal model for depression was formulated and fitted to data from both children and adolescents. Results in children indicated that vulnerability associated with the family environment and parenting was mediated through maternal depressive conditions and child attributional style, to influence depressive outcomes. Moreover, the risk effects of negative attributional style increased substantially in the presence of negative life events. Genetic factors made moderate contributions towards depressive symptoms in this age group and correlated with negative life events. A different set of results characterised the

adolescent group with little support for the mediation of distal familial risks through intermediate psychosocial and cognitive factors, and for interactions among these variables. However as with previous Chapters, a dominant role for genetic effects characterised the trajectory of depressive symptoms across time in this age group.

7.2. Background

Environmental influences comprise one domain of risk factor involved in the development of depression symptoms. Earlier research focussed on identifying specific candidates of social risk, with negative life events and chronic stressors emerging as important contributors to the development of child and adolescent depression, as with adults. A more recent shift in interest has been to move beyond documenting associations between individual predictors and depressive outcome, to exploring the mediating and moderating effects that may characterise inter-relationships between different variables. More specifically, risk effects associated with distal factors, such as familial adversity have been found to be mediated through more proximal vulnerability factors such as parenting practices to influence depression symptoms (Ellenbogen & Hodkins, 2004). In addition, the effects of certain vulnerability factors, (e.g. familial adversity) may also be moderated (exacerbated or attenuated) in the presence of predisposing factors (e.g. negative life events) (Goodyer, 1990). Examining the mediating and moderating effects between social variables may reflect different routes leading to depression (e.g. Burt et al, 2005; Cummings et al, 2005; Spence et al, 2002).

Parallel to these efforts are attempts to integrate psychosocial risk mechanisms within other theories of depression, most notably cognitive vulnerabilities and genetic liability (e.g. Goodman & Gotlib, 1999). Studies examining the relationship between cognitive and psychosocial factors have revealed that cognitive vulnerability may mediate the effects of familial chronic stressors on depression (McGinn et al, 2005). Furthermore

several theories, such as the reformulated learned helplessness theory, propose that cognitive vulnerability factors interact with negative life events to influence depression symptoms. Genetic variables have also been incorporated into recent studies addressing psychosocial risks on a phenotype, primarily to illustrate environmental mediation after controlling for genetic influence (e.g. Kim-Cohen et al, 2005). Although there are concerns that the assumptions held by these approaches are logically flawed (e.g. (Purcell & Koenen, 2005), considering genetic risk mechanisms with psychosocial factors may maximise the explanatory power of a phenotypic outcome through joint analysis of several variables (e.g. Kendler et al, 1993).

As these integrative studies have only been conducted in adult populations (Kendler et al, 1993), the purpose of the current analyses was to explore psychosocial and cognitive risk mechanisms on child and adolescent depression whilst assessing genetic risks. Path analysis was used to depict various pathways involving mediation and moderation between psychosocial and cognitive variables, occurring amidst genetic effects on depressive outcome. Key questions relating to the role of proximal psychosocial factors (parenting practices, maternal psychopathology) and cognitive vulnerability (attributional style) in mediating distal familial adversity (SES, maternal neuroticism, family stressors, marital conflict) were explored first. Second, the extents to which these proximal psychosocial and cognitive vulnerability factors interact with negative life events were also investigated. Finally, based on findings from previous Chapters, genetic risks including main effects on depression and attributional style, correlations and interactions with psychosocial risk variables were also included in these path models. Given the longitudinal design of each sample, inferences on possible causal effects could be drawn as well as assessing the combined effects of different risk factors.

7.3. Methods

7.3.1. Participants and Measures

A range of self- and parent-reported measures collected at different time-points in the G1219 and ECHO study were used to assess concurrent and predictive effects of psychosocial, cognitive and genetic factors on depression symptoms. These are summarised in Table 7.1. Depression symptoms collected at Wave 1 of the ECHO sample and Wave 3 of the G1219 sample formed the main outcome variables, and were reported using the Children's Depression Inventory (Kovacs, 1981) and the short Mood and Feelings Questionnaire (Angold et al, 1995) respectively.

Measures of psychosocial risk for the ECHO child sample included mother-reported data on family living arrangements or composition (twins living with both biological parents or not), SES and punitive discipline collected at age 7. Mother-reported data on previous depressive conditions (McGuffin et al, 1986) and child-specific negative life events (Coddington, 1984) from Wave 1 of the study were also used (see Section 3.3.2.3 for further details on how each measure was constructed). Psychosocial risk measures for the G1219 adolescent sample included mother-reported neuroticism and family stressors, and adolescent-reported maternal punitive discipline and negative life events. These were assessed using the Eysenck Personality Questionnaire (Eysenck et al, 1985), the Social Problems Questionnaire (Corney, 1988) and the List of Threatening Events (Brugha et al, 1985), the Negative Sanctions sub-scale (O'Connor et al, 2001) and the Life Event Scale for Adolescents (Coddington, 1984) respectively (see Section 3.3.1.3 for details on these measures).

Attributional style, an index of cognitive risk for depression symptoms was assessed in both samples using the Children's Attributional Style Questionnaire (Kaslow & Nolen-Hoeksema, 1991). Lower scores indicate a more negative attributional style.

Genetic liability for depression symptoms was defined continuously by multiplying the co-twin/sibling score and the genetic relatedness between the twin or sibling pair (1.0 for MZ twins; 0.5 for DZ twins and full siblings) (see Kim-Cohen et al, 2005).

Table 7.1: Summary of timeline at which variables were collected.

	Time 1	**Time 2**	**Time 3**
ECHO	Family Composition Socioeconomic Status Maternal Discipline	Maternal Depression Attributional Style Negative Life Events Genetic Risk Depression Symptoms[a]	
G1219	Maternal Neuroticism Genetic Risk Depression Symptoms Family Stressors	Maternal Discipline Genetic Risk Depression Symptoms Attributional Style	Negative Life Events Genetic Risk Depression Symptoms[a]

[a] This variable was used as the outcome variable

7.3.2. Statistical Analysis

Preparation of these data was conducted in SPSS. Descriptive statistics were performed by specifying a saturated model in Mx. All remaining analyses were carried out using structural equation modelling techniques of path analysis, and applied with the matrix algebra and fit functions available in Mx. As with previous analyses weighting variables to account for initial response bias and subsequent attrition were included in G1219 analyses (see Section 3.3.1.2). A similar weighting system was constructed from the ratio of the selection probability of proband families to that of control families in ECHO participants to account for the selection process used in this sample. Appendix B.9 gives an example Mx script for these models.

7.3.2.1. Descriptive analyses

A saturated model in Mx, which estimates the variance, covariance and means of measured variables, was fitted to raw data to examine mean group differences and phenotypic correlations between measures. Sex differences can be ascertained by comparing Model 1a which estimates one mean for males and one mean for females, with Model 1b which estimates one mean across the whole sample. Given that there were no expected mean sex differences in SES, family living arrangements, maternal neuroticism, family chronic stressors and genetic variables, these comparisons were not applied to these measures. Mean differences between zygosity groups were also not examined as the current analyses do not rely on differences in within-pair similarity among zygosity groups to estimate genetic and environmental parameters, and thus these effects were less pertinent to modelling procedures.

Phenotypic correlations with age were only reported for G1219 variables, given a restriction in age range in the ECHO sample. As with sex differences, age trends were not examined with regard to maternal neuroticism or family chronic stressors. Finally the expected phenotypic correlations between all variables were computed to assess different inter-relationships among risk factors, and with depression outcome.

7.3.2.2. Concepts of Path Analysis

The main set of analyses was conducted using path analysis. This technique assesses structural relations between observed variables, and is particularly appropriate when there are only single measures of each theoretical construct. Path analysis can be used to examine the effect of one or more dependent variables (predictors) on an independent variable (criterion) by estimating direct causal paths between them. When there are multiple predictors in path analysis, the effects of each individual predictor on the criterion are adjusted for inter-correlations among predictors. Thus this method also

controls for non-causal aspects of the observed correlation between a predictor and a criterion variable, which may arise from spurious associations with other predictors. In addition to direct effects, indirect paths involving mediation and interactions between predictor variables can also be incorporated in this framework.

Mediation occurs when the effects of one predictor operate via another predictor (called a mediator variable) on the criterion variable. Support for mediation in path analysis can be derived by establishing significant associations between the predictor and the mediator, and the mediator and the criterion variable, whilst adjusting for any direct effects the predictor has on the outcome variable. Thus, a predictor may be involved in both direct as well as indirect pathways to depression.

An interaction occurs when the effects of a predictor is dependent on another predictor (called a moderator variable) on the criterion variable. The effects of the predictor may be exacerbated or attenuated in the presence of the moderator. Possible interactions between variables can be assessed by including their product as a third predictor on the criterion variable within path analysis. The level of significance of this effect determines whether an interaction is present.

7.3.2.3. Model Formulation

Based on these principles, models depicting different direct, indirect and interaction paths between variables were formulated for the ECHO and G1219 data and represented in diagrammatic form (Figures 7.1 and 7.2). Of note, these models are not identified in their current forms, that is, it was not theoretically possible from the information available to derive unique estimates of each path coefficients simultaneously. Thus separate models had to be conducted to test specific mediation and moderation hypotheses, and are described in more detail in the next section.

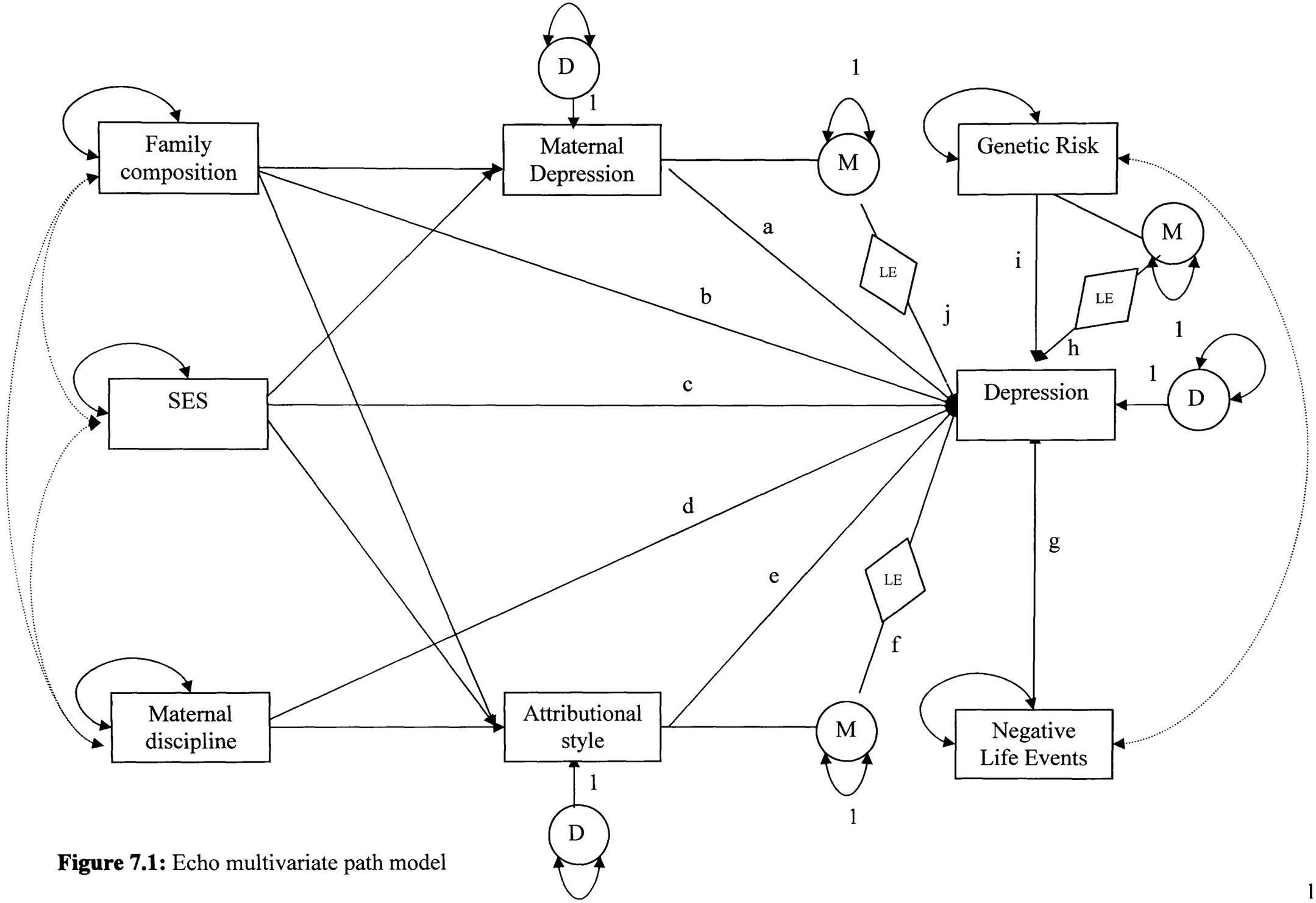


Figure 7.1: Echo multivariate path model

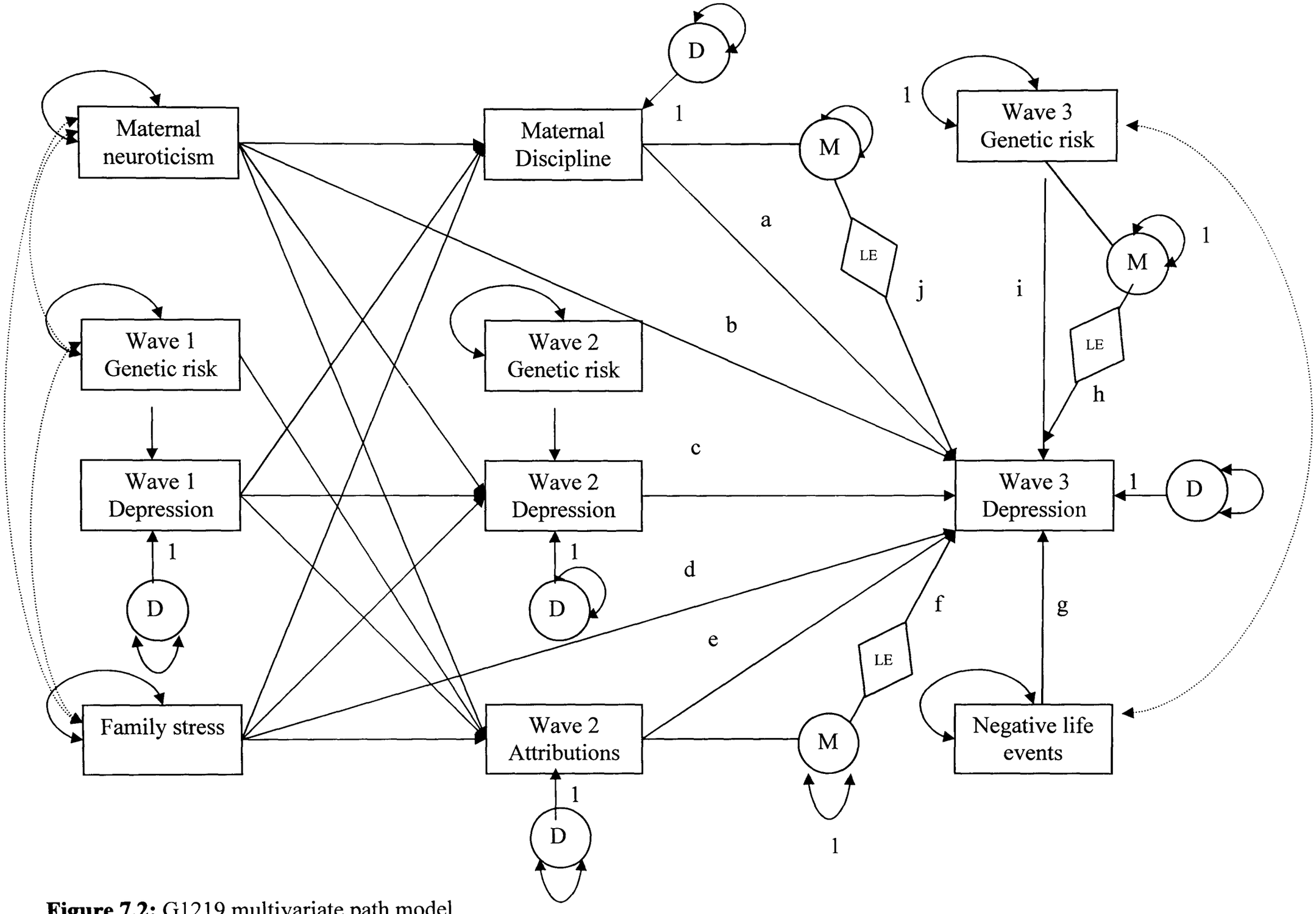


Figure 7.2: G1219 multivariate path model

The positioning of variables in both diagrams is based upon the time sequence at which variables were collected. The main outcome variable is represented at the far right of the figure with longitudinal and concurrent predictor variables represented accordingly. Mediator variables are those depicted in the middle of each diagram, and are both predictor variables as well as criterion variables. Predictor variables qualify as mediator variables if they were collected prospectively (or concurrently) with the predictor variable and prior to (or concurrently) with the criterion variable. The assessment of predictor, mediator and criterion variables at distinct time-points provides a measurement framework which justifies the strongest interpretation of causal effects on depressive outcomes. Although data from the G1219 study was consistent with this framework, the ECHO data consisted of only two time-points.

Using notation from path analysis (see Kline, 2004 for a review), observed variables are drawn as rectangles, direct paths between variables as single-headed arrows and covariance between variables (or correlations if standardised variables) as double-headed (dotted) arrows. Interactions between a predictor and a moderator on the criterion variable are depicted by a diamond shape appearing on an indirect path from the predictor to the criterion via a latent variable, M. The effect of this path on the criterion variable reflects the product of the predictor and moderator variables, that is, their interactive effect.

The variance of exogenous variables and residual variances of endogenous variables are also estimated in path models. Exogenous variables are observed variables whose causes are not specified by the model but instead are assigned as causes of other variables. The variances of exogenous variables are denoted by double-headed curved arrows which exit and re-enter the same variable. Endogenous variables are those where presumed causes are defined by the model. As not all causes of endogenous variables are included in the model, a 'disturbance' to account for residual variance of the

endogenous variable is also specified. As this source of variance is unmeasured, it is represented as a circle, whose variance is also estimated. Disturbances are linked to the endogenous variable through a single headed arrow path which is assigned a scale or metric of 1.0. The variance of the interaction term is also estimated.

7.3.2.2. Path analysis: Testing hypothesised paths

Direct, indirect and interactive paths and correlations illustrated in the path diagrams in Figures 7.1 and 7.2 were specified and estimated using maximum likelihood methods available in Mx. Of specific relevance to the hypotheses outlined in this Chapter are the extents to which certain psychosocial factors (maternal depression in the ECHO sample and maternal punitive discipline in the G1219 sample) and cognitive risk factors (attributional style) mediate other sources of 'distal' familial vulnerability collected at earlier time-points (family composition, SES and maternal discipline in the ECHO sample and maternal neuroticism and family chronic stressors in the G1219 sample) on depressive outcomes across time. A second question was whether the effects of these psychosocial and cognitive factors also increased in the presence of negative life events.

These mediating and moderating pathways were explored whilst simultaneously assessing genetic risks on the phenotype. In the G1219 sample, genetic effects on depression symptoms were included at all three time-points allowing for both genetic continuity (mediated through depression measures) and new genetic effects at each time-point to be modelled simultaneously, consistent with findings from Chapter 4. Potential gene-environment correlations and interactions as suggested by the results of Chapter 5 were also included. Thus correlations and direct effects between genetic and psychosocial factors such as maternal neuroticism, family chronic stress, maternal punitive discipline and negative life events were specified. In addition, an interaction effect between genetic risk and negative life events was also incorporated.

Genetic risk could only be specified at one time-point in the ECHO study and this was allowed to correlate and interact with negative life events, to reflect processes of gene-environment interplay. Findings from Chapter 6 of genetic contributions to attributional style and of the reciprocal relationship between attributional style and depression in adolescence were also depicted in the model for the G1219 sample. Correlations between variables collected at the same time-point were also included in both samples based primarily on findings in the existing literature that aspects of the familial environment may be correlated. In the final version of the G1219 path model, correlations between the residual variances of maternal punitive discipline, Wave 2 depressive symptoms and attributional style were also specified. This was to account for any other shared causes between these variables which were not represented in the current model, and could potentially explain their observed phenotypic correlations. Of note, correlations between variables can only be included if both are exogenous variables, or both are endogenous variables.

As with previous model-fitting analyses, individual paths involved in these mediating and moderating paths can be tested for significance, by excluding the path coefficient from the model and assessing change in fit. However as noted earlier, neither model illustrated in Figures 7.1 nor 7.2, is identified. In fact, according to criteria for model identification, which is based on the number of endogenous variables specified in each model (Maruyama, 1998), the total number of paths on each endogenous variable cannot exceed 8 for the ECHO path model or 9 for the G1219 path model. As seen in the diagram, this rule is violated for the depression outcome variables, as these are predicted by the greatest number of variables in each model. Thus four separate models were used to test the different components of each path model.

Model 1 of the ECHO sample examined the significance of the interaction between maternal depression and negative life events on depression outcome (path j), whilst

estimating all other direct paths and correlations between variables as illustrated in Figure 7.1, with exception to paths f and h. Models 2 and 3 examined the interaction between attributional style and negative life events (path f), and the interaction between genetic factors and negative life events (path h) on depression symptoms respectively. Thus Model 2 estimated all paths except for h and j, whereas Model 3 estimated all paths except for f and j. Model 4 included only direct effects and correlations between variables, thus omitting paths involving interactions (f, h and j) from analysis. As Model 4 systematically tested path coefficients involved in direct effects, it explored the mediation pathways on depression hypothesised earlier.

Models 1, 2 and 3 of the G1219 sample were comparable to those specified for the ECHO sample, and tested for interactions between maternal punitive discipline and negative life events (path j), attributional style and negative life events (path f) and genetic risk and negative life events (path h) on depression outcome respectively, whilst including all direct effects and correlations represented in Figure 7.2. In other words, paths f and h were omitted in Model 1; paths h and j from Model 2; and finally paths f and j from Model 3. Model 4 explored the remaining mediation hypotheses by incorporating all direct paths and correlations depicted in Figure 7.1 but not path coefficients associated with moderation pathways (f, h, j).

Only significant paths from each model were retained to produce a more parsimonious solution. From this, path estimates and the combined effects of all significant pathways were assessed. As these analyses were conducted on standardised variables, the magnitude of path estimates between variables was comparable. The proportion of variation in depressive outcomes predicted by each model was computed from the difference between the estimated residual variance of the depression variables and unity. As path analyses do not directly estimate error variance, path coefficients include measurement error. The final solutions were compared to saturated models to derive fit

indices. Initial model-fitting analyses were conducted on half of each sample, to control for the non-independence of data collected from related individuals. However due to less power when using only half the sample, and given that effect sizes of parameter estimates were similar in both halves, current results were for the whole sample.

7.4. Results

7.4.1. Descriptive Statistics

Means, standard deviations and number of participants with available data, for depression, attributional style and psychosocial measures at each time-point are presented in Table 7.2 across the whole sample or by sex if significant mean differences between males and females were found.

As reported previously, there were significant mean differences between depression symptoms at all three time-points in the adolescent sample and on attributional style in both samples (Chapter 4 and 6). These results showed that females consistently reported more symptoms in adolescence, but contrary to expectations males possessed more negative attributional styles in both childhood and adolescence. Results from Chapter 5 indicate that there were no significant mean differences in maternal punitive discipline, as reported by the adolescents of the G1219 sample. Comparisons between sub-models testing for sex differences in the current analyses, demonstrate that males and females report comparable numbers of negative life events in both adolescence and childhood ($\Delta\chi^2(2) = 1.20$, p = n.s. for ECHO and $\Delta\chi^2(2) = 3.77$, p = n.s. for G1219). In comparison, significant sex differences in maternal punitive discipline in the child sample were found, with mothers reporting harsher disciplinary tactics with their male offspring ($\Delta\chi^2(1) = 16.45$, $p < 0.001$).

Table 7.2: Descriptive statistics for self- and parent-reported measures of depression symptoms, cognitive and psychosocial measures collected at each time-point in the ECHO and G1219 studies.

Study (Time-point)	Study variables	Number	Mean[a] (SD[b])	
			Males	Females
ECHO (T1)	Family Composition	588	1.11 (0.33)	
	Socio-economic Status	514	0.27 (0.70)	
	Maternal Punitive Discipline	575	0.42 (0.96)	-0.10 (1.05)
ECHO (T2)	Attributional Style	537	3.95 (3.23)	4.89 (2.86)
	Maternal Depression	502	1.17 (1.55)	
	Negative Life Events	559	0.33 (0.60)	
	Depression Symptoms	575	9.74 (6.93)	
G1219 (T1)	Maternal Neuroticism	3204	4.96 (3.11)	
	Depression Symptoms	3619	6.21 (5.20)	7.59 (6.11)
	Family Stressors	3530	1.56 (1.89)	
G1219 (T2)	Maternal Punitive Discipline	2489	7.20 (3.79)	
	Depression Symptoms	2631	6.67 (5.57)	9.10 (7.23)
	Attributional Style	2563	4.16 (3.30)	4.47 (3.27)
G1219 (T3)	Negative Life Events	1482	1.93 (1.85)	
	Depression Symptoms	1591	5.00 (4.73)	7.06 (5.52)

[a] Means and standard deviations are reported separately for males and females if significant sex differences in means or variance were demonstrated.

Analyses from previous Chapters have indicated that correlations between age and depression symptoms and attributional style are small and non-significant for all time-points in the adolescent sample (all r's < 0.05, p = n.s.) (Chapters 4 and 6). In comparison, age correlated significantly with maternal punitive discipline ($r = -0.16$, $p < 0.001$) with older adolescents reporting less punitive discipline (Chapter 5). The current analyses show that the number of negative life events reported at Wave 3 in the G1219 sample does not vary with age ($r = 0.02$, p = n.s.). Mean effects of age were regressed from the variables, before standardising.

Phenotypic correlations between all variables in each sample are presented in Table 7.3a and 7.3b. The main outcome depression variable is listed first in each table, thus this column reflects the associations between different risk factors and the phenotype. Males and females showed comparable correlation matrices in the ECHO data, and these are presented for the whole sample. The expected correlation matrices of males and females could not be constrained to be the same in the adolescent sample ($\Delta\chi^2(77) = 212.45$, $p < 0.001$) indicating possible sex-effects in the inter-relationships among variables. Correlations are therefore presented separately across sex, with male data below the diagonal and female data above the diagonal.

Table 7.3a: Phenotypic correlations between all variables in ECHO.

	DEP	**FAM**	**SES**	**MPD**	**MD**	**ATT**	**GR**	**NLE**
DEP	**1.00**							
FAM	0.18	**1.00**						
SES	-0.15	-0.32	**1.00**					
MPD	0.15	0.04	-0.19	**1.00**				
MD	0.16	0.18	-0.09	0.19	**1.00**			
ATT	-0.46	-0.09	0.09	-0.08	<0.001	**1.00**		
GR	0.21	0.14	-0.14	0.12	0.08	-0.12	**1.00**	
NLE	0.11	0.31	-0.13	0.03	0.15	-0.07	0.13	**1.00**

DEP = Depression (main outcome variable); FAM = Family Composition; SES = Socioeconomic Status; MPD = Maternal Punitive Discipline; MD = Maternal Depression; ATT = Attributional Style; GR = Genetic Risk; NLE = Negative Life Events

Depression symptoms at Wave 1 of the ECHO study was significantly associated with a more negative attributional style, increased genetic risks and more negative life events. Previous maternal depressive conditions, lower SES, increased maternal use of punitive discipline and living in a step- or single-parent family also showed modest but significant associations with depression symptoms.

Table 7.3b: Phenotypic correlations between all variables in G1219.

	W3D	MN	W1G	W1D	FAM	MPD	W2G	W2D	ATT	W3G	NLE
W3D	**1.00**	0.11	0.31	0.42	0.05	0.27	0.34	0.58	-0.35	0.37	0.38
MN	0.12	**1.00**	0.19	0.22	0.38	0.19	0.17	0.19	-0.10	0.16	0.17
W1G	0.19	0.13	**1.00**	0.61	0.18	0.18	0.71	0.45	-0.30	0.49	0.25
W1D	0.45	0.18	0.38	**1.00**	0.18	0.31	0.47	0.57	-0.42	0.38	0.31
FAM	0.01	0.40	0.15	0.20	**1.00**	0.17	0.15	0.10	-0.04	0.08	0.14
MPD	0.12	0.03	0.05	0.18	0.13	**1.00**	0.14	0.35	-0.31	0.12	0.22
W2G	0.17	0.13	0.53	0.23	0.07	0.05	**1.00**	0.50	-0.27	0.55	0.26
W2D	0.48	0.10	0.23	0.55	0.06	0.21	0.25	**1.00**	-0.45	0.43	0.34
ATT	-0.23	-0.11	-0.10	-0.31	-0.10	-0.20	-0.10	-0.35	**1.00**	-0.22	-0.22
W3G	0.29	0.12	0.37	0.14	0.04	-0.04	0.40	0.18	-0.12	**1.00**	0.26
NLE	0.36	0.11	0.13	0.24	0.12	0.19	0.10	0.23	-0.14	0.19	**1.00**

Figures below the diagonal are for males and those above the diagonal are for females. W3D = Wave 3 Depression (main outcome variable); MN = Maternal Neuroticism; W1G = Wave 1 Genetic Risk; W1D = Wave 1 Depression; FAM = Family Stressors; MPD = Maternal Punitive Discipline; W2G = Wave 2 Genetic Risk; W2D = Wave 2 Depression; ATT = Attributional Style; W3G = Wave 3 Genetic Risk; NLE = Negative Life Events

Depression symptoms at Wave 3 of the G1219 study was significantly associated with increased genetic risks, previous depression symptoms, a negative attributional style and negative life events. Increased use of maternal punitive discipline also significantly correlated to depression outcome at Wave 3, although this association was somewhat larger in females compared to males. Finally, distal psychosocial factors collected at Wave 1, including increased levels of maternal neuroticism and family chronic stressors had modest associations with Wave 3 depression symptoms.

7.4.2. Path Analyses

The next step was to utilise path analysis to estimate direct causal paths and correlations between variables illustrated in Figures 7.1 and 7.2 from the correlation matrices presented in Tables 7.3a and b. Path coefficients derived from structural equation

modelling techniques are adjusted for inter-correlations between all measured variables, thus reducing any spurious effects which may confound causal effects between variables. Due to issues of model identification, four separate models were examined for each sample to test all paths depicted in the diagrams.

Results from the significance testing of the paths in each Model are presented in Table C.9 of the Appendix. Direct paths estimated in both samples were first constrained across males and females to examine possible sex-differences in these models. As there was no significant reduction in fit associated with these constraints, results are presented for the whole sample for both ECHO and G1219. Parameter estimates from the models of best-fit, which contain only significant path coefficients (or those that showed a non-significant trend) are presented in Figures 7.3 and 7.4 with fit statistics from comparison with saturated models.

Both models show very poor overall fit to the data. These were: -2LL = 16147.05, df = 5963, $\chi^2(130) = 558.93$, $p < 0.001$, AIC = 298.93, RMSEA = 0.11 for the Echo path model and -2LL = 58118.85, df = 22321, $\chi^2(196) = 2109.05$, $p < 0.001$, AIC = 1717.05, RMSEA = 0.13 for the G1219 model. Yet reasonable proportions of the total variance of depressive outcome were explained by each model: 25.43% for ECHO data and 29.17% for G1219 data. Interpretations of the path estimates from each model are discussed together, under three sections of: the mediation of distal familial risk factors, moderation of proximal risk factors and genetic risk mechanisms. In the first two sections, results from the child sample will be presented first. As the third section on genetic risk mechanisms were studied in more detail in the G1219 sample, the results of both samples are discussed together.

Figure 7.3: Path estimates from the Echo multivariate model

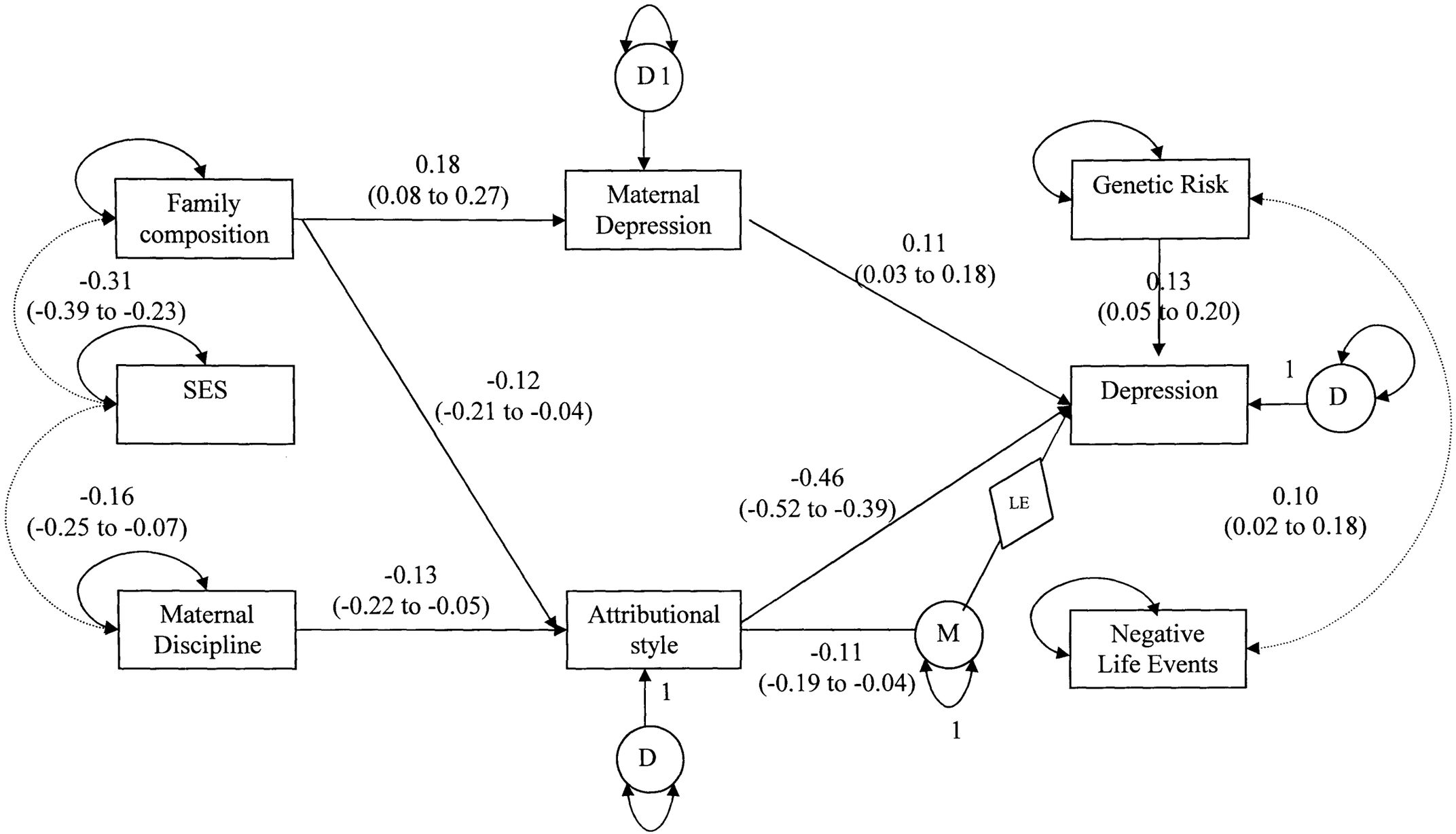
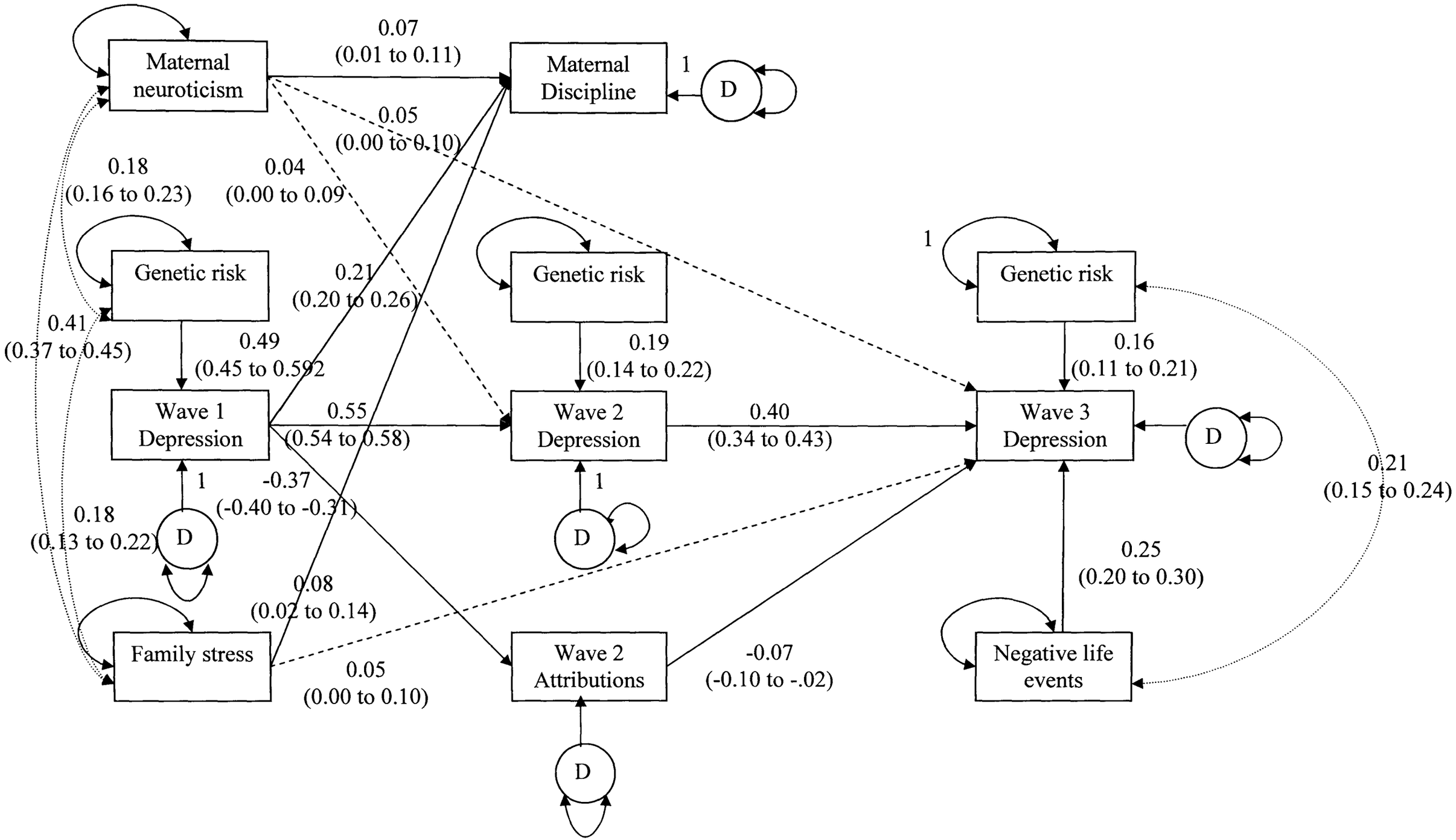


Figure 7.4: Path estimates from the G1219 multivariate model



7.4.2.1. Mediation of distal familial psychosocial risks

The first set of hypotheses examined whether proximal psychosocial and cognitive risk factors mediated distal familial risk factors on depressive outcome whilst also assessing genetic risks. Results from the ECHO path analyses supported some of the mediational hypotheses. Family composition, which indicates whether children reside with both biological parents, and thus indexes vulnerability associated with being in a step- or single-parent family did not influence depression symptoms directly. Instead it predicted both maternal depression and a negative attributional style (0.18 and -0.12), which in turn contributed towards depression symptoms (0.11 and -0.46), yielding a total indirect effect of: (0.18 x 0.11) + (-0.12 x -0.46) = 0.08. Similarly, the risk effects of maternal punitive discipline on depression outcome were mediated entirely through attributional style. The total indirect effect of this route was: -0.13 x -0.46 = 0.06. Socio-economic status, which had a modest correlation of -0.15 with depression (see Table 7.3a), did not continue to predict the phenotype, once its correlations with family composition and maternal punitive discipline had been accounted for. Thus, its effects on depression may be mediated entirely through its associations with other social risks.

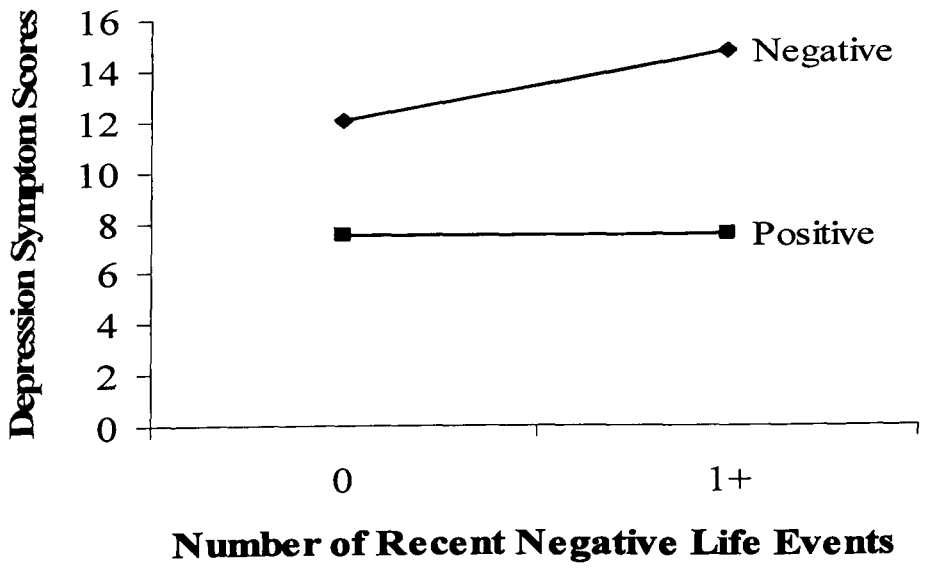
Results from the G1219 sample were less clear. Both maternal neuroticism and family chronic stress, which reflect distal risks associated with the family environment, predicted a more proximal source of psychosocial vulnerability, maternal punitive discipline (0.07 and 0.08). However this hypothesised mediator did not in turn influence depressive outcome once inter-correlations with other predictor variables were adjusted. Attributional style was also proposed as a mediator of distal sources of familial vulnerability on depressive outcome but neither maternal neuroticism nor family chronic stress predicted this cognitive factor. Thus no indirect pathways by which distal risk effects were mediated through maternal punitive discipline and attributional style on the phenotype were identified. Instead, both maternal neuroticism and family chronic

stress showed non-significant trends for predictive effects towards depressive outcome at Wave 3 and for maternal neuroticism towards Wave 2 symptoms too, suggesting possible direct but weak effects on the phenotype.

7.4.2.2. Moderation of proximal risk factors

The second set of hypotheses focussed on moderation of the intermediate psychosocial factors and attributional style on depressive outcome by negative life events. Results from the ECHO path analyses showed that there was no significant main effect of life events on depression symptoms, but both maternal depression and attributional style were key predictors of depressive outcomes. The interaction between negative life events and maternal depression symptoms was non-significant, but a significant interaction between negative life events and attributional style emerged. To explore this further, a median split was used to divide the sample into negative and positive attributional styles, and the mean depressive scores of each group was examined as a function of the presence or absence of negative life events. Results displayed in Figure 7.5 show that in addition to main effects of negative attributional style on depressive symptoms, these risks were significantly accentuated in the presence of life events.

Figure 7.5: Depression symptom scores as a function of attributional style and negative life events



In the G1219 sample, there was a significant main effect of negative life events on depressive outcome (0.25) but main effects of maternal punitive discipline were negligible whilst those associated with a negative attributional style were weak (-0.06). No significant interactions between these variables were demonstrated.

7.4.2.3. Genetic Risk Mechanisms

The third set of findings examined genetic risk mechanisms on depressive symptoms including their main effects concurrently and across time, their interplay with environmental risk factors and their influence on cognitive vulnerability. Genetic risks were significant predictors of the phenotypic outcome in both samples. Moreover, both 'stable' and 'new' genetic effects could be differentiated in the G1219 sample. Specifically, depression symptoms at Waves 2 and 3 were influenced by genetic risks assessed at Wave 1, mediated through the phenotypic continuity in symptoms between Waves. Additional genetic risks estimated at these later Waves were therefore suggestive of 'new' influences, independent from those assessed at Wave 1. Thus Wave 2 depression symptoms were predicted by a mixture of 'stable' genetic effects from Wave 1 and 'newer' effects emerging at this time-point, whilst Wave 3 depression symptoms reflected the additive effects of stable genetic factors from Waves 1 and 2, and 'new' influences unique to this wave.

Significant correlations between genetic risk variables and various psychosocial factors were also demonstrated in both samples, attesting to the presence of gene-environment correlations. Thus genetic risks were positively associated with negative life events in both the ECHO and G1219 path models. Additionally, in the G1219 sample, maternal neuroticism and family chronic stress correlated significantly with genetic risk assessed at Wave 1; and genetic effects influenced maternal punitive discipline indirectly through Wave 1 depression symptoms. Contrary to expectations, there were no interactions

between genetic risks and negative life events in either sample. Finally, moderate genetic effects on attributional style were mediated through Wave 1 depression symptoms (0.49 x -0.37 = 0.18), suggesting some shared genetic variance among these two variables in the G1219 sample.

7.5. Summary

The path models analysed in the present study aimed to gain insight into the different pathways through which psychosocial, cognitive and genetic risk factors may be expressed during childhood and adolescence. In particular, specific risk mechanisms focussing on the mediation of family social adversity by intermediate psychosocial and cognitive risk factors and the moderation of intermediate psychosocial vulnerability factors by predisposing life events were explored, whilst simultaneously accounting for genetic risk mechanisms on depressive outcome. Although there were clear differences in results obtained from each sample, differences in the study variables and design made direct comparisons between age groups unfeasible. As such findings from each sample are summarised separately with results from the child sample presented first.

Several indirect routes by which familial adversity influenced depressive outcomes were evident in the child sample. First, vulnerability associated with living in a step- or single-parent family and punitive parenting did not have direct effects on depressive outcome but instead influenced intermediate psychosocial and cognitive risk factors, which mediated these risks on the phenotype. More specifically, living in a step- or single-parent family increased both maternal depressive conditions and the presence of negative attributions in children, whilst punitive parenting influenced negative attributions only. In turn both maternal depression and negative attributional style predicted increases in depressive symptoms in children. Moreover the risks associated with attributional style were further exacerbated in the presence of negative life events.

Finally in addition to the effects of these psychosocial and cognitive risk mechanisms there were also moderate genetic effects on depressive outcome too, of similar magnitude to that reported in univariate analyses of Chapter 4.

There was little evidence for the hypothesised mediation and moderation pathways on depressive outcome in the adolescent sample. Thus although maternal neuroticism and family chronic stress predicted maternal punitive discipline, this latter factor did not predict depressive symptoms directly once other concurrent predictors were included in the model. Similarly, despite showing significant correlations with attributional style, neither maternal neuroticism nor family chronic stress predicted this cognitive mediator in the full path model. Interactions between negative life events, and maternal punitive discipline and attributional style were also non-significant.

Perhaps the strongest finding in the adolescent sample was to reinforce the important role of genetic factors in accounting for variation in the phenotype. Wave 3 depressive outcome was influenced by 'stable' genetic effects assessed at earlier time-points and 'new' genetic effects emerging at this time-point. There was also evidence of genetic influences on several psychosocial risk variables including maternal neuroticism, family chronic stress, maternal punitive discipline and negative life events. However an interaction between genetic risk and negative life events was not supported by the data. Of note, the life events data and genetic risk variable used to test for interaction were collected at a different time-point to those analysed in Chapter 5. Thus this result is not in direct contradiction to that reported earlier, which was derived using an alternative analytical technique. Finally, there was also some confirmation of shared genetic variance between depression symptoms and attributional style, mediated through their reciprocal effects.

The current sets of analysis probably represent the first wave of empirical attempts to fit data from a wide variety of risk measures to a theoretical model encompassing psychosocial, cognitive *and* genetic risks in childhood and adolescence. Undoubtedly their strengths lie in the large sample sizes needed for the use of path analyses; the number of risk measures available from both parent-reports and self-reports; and the longitudinal designs of each study, which are most appropriate for drawing conclusions on directional effects. However several limitations also need to be considered, most obviously the apparent poor fit of the models to the data. Although this may in part be reflective of the large sample sizes, the RMSEA index which corrects for numbers of participants remained large, indicating bad fit. A justification for this is that as the number of variables in a model increases, the number of cross-variable covariances also increases, and it becomes more difficult to obtain a set of model parameters that satisfy all the observed covariances of the data. As most studies in the literature opt for the use of multiple regression to test such hypotheses, large multi-measure models are rare and as a consequence, there are few studies to compare the acceptability of the level of fit.

Another index of how well such models fit the data is the degree to which they explain variation on a phenotypic measure. In the current study, both models only accounted for moderate proportions of the variance, compared with almost 50% in the previously cited adult sample (Kendler et al, 1993). A possible reason is that different informants were used in the current study, thus rater differences may lower phenotypic associations. In addition the current list of predictors in neither sample was exhaustive. For example no extra-familial sources of social risk were incorporated in either model. This could explain why many of the predicted mediation and moderation pathways in adolescence were not found. Stressors related to peer and social relationships, academic and early employment achievements may have larger impact on the development of depressive symptoms and negative attributions in this age group. In comparison, younger children

may be more vulnerable to risks associated with the family environment, a suggestion that is compatible with the finding of generally larger shared environmental effects in this age range. Future studies should tailor path models on the basis of age-normative stressors, a theme which has not been emphasised enough in existing literature.

A third drawback of the current samples was the rather crude index of genetic effects used in both path models. This was literally the product of the co-twin score and genetic relatedness (indexed by zygosity group), and quite unlike the more sophisticated genetic latent variable modelled in previous Chapters. This simplistic index may account for the lack of gene-environment interaction demonstrated in the adolescent sample, conflicting somewhat with findings in Chapter 5. Nevertheless, main effects of genetic variables on depression symptoms were significant in both samples. Whilst some have argued that the inclusion of such 'genetic' variables provide a rigorous test of 'pure' environmental mediation, whereby the remaining significant effects in the model are 'free' from genetic influence (e.g. Kim-Cohen et al, 2005), others have deduced logical flaws in the assumptions of this approach (Purcell & Koenen, 2005). First, only genetic effects on depression symptoms were specified in the current path models. Although many of the other variables are also likely to be influenced by genetic effects, these were not modelled specifically. One of the reasons for this is the use of measures that are obligatory shared among twins (or siblings), that is, the same values are reported for each member. In this scenario, even if a variable was genetically influenced (for example, mother's neuroticism), the degree of similarity among MZ and DZ (and FS) pairs would be identical, at 1.0, as they are the same for both members of a pair. Given that there are no differences in similarity between zygosity groups, genetic effects cannot be estimated for such variables. Without adequately assessing genetic influences on such social risk variables, one cannot control for all genetic influences in the model, and in turn would not be justified in inferring that the association between a social risk

variable and depression symptoms represented 'pure' environmental risk. Thus, interpretations of such models should be considered carefully.

A fourth design-related caveat associated with these models is that measurement error is not specifically accounted for. In path analysis, where there is only a single indicator of most theoretical constructs, random error is included in the estimates of path coefficients between variables, thus confounding 'true' predictive effects. Fifth, effect sizes of stressors, cognitions and their interactions were fairly small, with prior symptom levels and to a lesser degree genetic risk explaining the bulk of the variance, particularly in the G1219 model. This finding is however not unique to the current models, but is relatively common among predictive modelling or regression analyses. Finally, despite boasting large sample sizes, statistical power for these analyses was still rather limited. Although preliminary analyses were conducted on half the sample (to take into account the non-independence of data from related individuals), many of the hypothesised estimates were non-significant, despite effect sizes remaining largely the same in both halves of the sample. Thus the final path models were re-analysed using data from all participants, which does not correct for familial clustering.

In summary, although interpretations and generalisations of these models are rather limited by their poor fit to the data, the methodological framework used provides a culminating point for the integration of findings from separate research disciplines, and their implications are discussed in Chapter 8.

Chapter 8: Discussion and Conclusions

8.1. Overview

The aims of Chapters 4, 5, 6 and 7 were to explore genetic, cognitive and psychosocial risk mechanisms on depression symptoms in children and adolescents. Consistent themes which have emerged across these Chapters include an increasing focus on how different domains of risk factor relate to one another and second how different risks may be expressed at distinct stages in development to account for phenotypic changes across time. In this concluding chapter, a summary of each Chapter is presented, followed by a discussion of general methodological caveats associated with the overall study design. As these limitations may somewhat restrict the scope with which these findings are interpreted, tentative implications on the different routes by which genetic, cognitive and psychosocial factors influence depressive symptoms across childhood and adolescence are presented next. The Chapter concludes with a brief discussion of future directions and implications for clinical practice.

8.2. Summary of Results

This thesis utilised data from two samples to address four main research questions. This section provides an overall summary with respect to each set of findings.

8.2.1. Genetic Effects on Child and Adolescent Depression Symptoms

The first set of hypotheses related to the nature of genetic and environmental effects on depression symptoms in relation to age and sex effects, developmental change, and the operation of these factors in extreme groups.

Results of this study generally supported previous research. Genetic effects were largest among the adolescent sample, at all three time-points and smaller in childhood, where

their effects fell slightly from middle to late childhood (ages 8 to 10). Shared environmental variance was largest at age 10 and decreased across adolescence. Sex-effects were not studied in the child sample due to power constraints, and none were documented in adolescence at any time-point with the exception of variance differences.

The second set of findings showed the role of 'stable' genetic factors in contributing towards continuity of depressive symptoms across time during adolescence. In addition 'new' genetic influences emerged at Wave 2, a time-point corresponding to mid-adolescence for most of the sample. Continuity of shared environmental effects was more characteristic of the younger aged sample, with 'new' effects emerging at ages 7 and 8, which influenced symptoms at aged 10. For both age ranges, there were new non-shared environmental effects at each time-point, but these contributed very little to subsequent continuity.

The final set of results showed non-significant trends of increased shared environmental and decreased genetic effects among extreme group membership in both children and adolescents. Sex-effects were evident at Wave 2 of the G1219 sample. These showed that shared environmental effects were more influential among females reporting more severe forms of depression, compared to males.

8.2.2. Genetic-Environmental Interplay on Adolescent Depression

The second set of research hypotheses focussed on two mechanisms by which genetic effects may be expressed in interplay with environmental factors. Gene-environment correlations and gene-environment interactions were examined in adolescence in relation to negative life events and maternal punitive discipline. This age range was chosen due to findings of increased genetic effects and large non-shared environmental variance in Chapter 4. Furthermore, new genetic effects had been documented at the time-point selected for these analyses.

In support of previous research, the results of this study demonstrated significant genetic influence on negative life events and maternal punitive discipline, implicating gene-environment correlation. Moreover there was genetic overlap between depression symptoms and each environmental risk factor, suggesting that genetic risks on the phenotype are expressed through exposure towards high-risk environments of negative events and maternal punitive discipline.

The next step of analyses provided support for gene-environment interaction after controlling for gene-environment correlation. Specifically genetic variance increased across levels of both negative life events and maternal punitive discipline. Genetic effects which contributed to maternal punitive discipline were distinct to those that were moderated by this risk factor. In comparison, the same genetic factors were involved in both correlation and interaction with negative life events. Finally, some support for interactions among environmental factors, such that non-shared environmental variance also increased with higher levels of maternal punitive discipline was found.

8.2.3. Attributional Style as a Cognitive Risk Factor of Depression Symptoms

The third set of hypotheses addressed various issues relating to attributional style as a vulnerability factor of depression. Genetic and environmental contributions to attributional style and its association with depressive symptoms was examined and compared in children and adolescents. Explanations of attributional style as a concurrent, causal or consequential influence on depression were also addressed.

This study supported several age-related trends in the genetic and environmental architecture of attributional style and its association with depression symptoms. Attributional style in adolescence was influenced primarily by genetic and non-shared environmental effects whereas more mixed results were reported in childhood due to the lower statistical power available to distinguish between genetic and shared

environmental effects. However the effect sizes suggest that shared but predominantly, non-shared environmental variance may characterise this cognitive factor in childhood.

The second set of findings demonstrated that despite showing roughly similar phenotypic correlations, the extent of shared genetic and environmental liabilities accounting for this association was different between childhood and adolescence. Adolescent attributional style and depression symptoms shared common genetic and non-shared environmental influences, which also accounted for their phenotypic relationship. Interestingly, the extent of shared genetic variance and the proportion by which it explained their phenotypic correlation increased with age. Thus in late-adolescence, common genetic factors contributed to roughly two thirds of the observed correlation, relative to about a third by common non-shared environmental effects. Delineating the sources of shared liability between childhood attributional style and depressive symptoms was more problematic. The only significant result was that these factors had common non-shared environmental influences, which also contributed towards their observed correlation.

The final set of results supported a reciprocal interlocking relationship between attributional style and depression symptoms in adolescence. In addition to concurrent associations between these measures, attributional style also predicted depressive symptoms across time. However the converse effect was true with depression symptoms also contributing to later negative cognitive styles.

8.2.4. Psychosocial Risk Mechanisms of Child and Adolescent Depression

The last set of hypotheses assessed the inter-relationships between specific psychosocial risk factors and depression symptoms in childhood and adolescence. A concurrent aim was to simultaneously include cognitive and genetic explanations of the phenotype within the analytical framework to assess the combined effects of different domains of

risk factor. Thus this Chapter incorporated findings from previous Chapters of the role of genetic factors and attributional style in addition to testing newer hypotheses on the mediating and moderating mechanisms, governing the inter-relationships among psychosocial, cognitive and genetic variables.

The current study supported several distinct routes to depressive outcome in children. First, risks associated with living in a step or single-parent family were mediated entirely through maternal emotional symptoms and attributional style, on depression symptoms. Second, attributional style also mediated the effects of maternal punitive discipline on depression symptoms. Third the effects of attributional style on depression symptoms increased in the presence of life events. Finally, genetic factors accounted for a modest but unique proportion of variance on depressive symptoms.

Results from analyses conducted on the adolescent sample were less supportive of the hypothesised mediation and moderation pathways. Although maternal neuroticism and family chronic stress influenced maternal punitive discipline, this proposed mediator did not significantly predict later depressive symptoms once previous depression and genetic risks had been accounted for. Similarly, whilst attributional style, the second proposed mediator contributed towards depression symptoms, neither source of distal psychosocial risk predicted attributional style. Interactions between negative life events and these mediators were also not significant.

However in support of previous findings, strong genetic effects, including stable and new factors emerged at all three time-points. These influenced concurrent symptoms and the stability of symptoms over time. Moreover correlations between genetic effects and several psychosocial risk factors were demonstrated, supporting gene-environment correlation. In comparison, gene-environment interactions were not found. Finally,

reciprocal effects between attributional style and depression across time were reinforced by these results, with suggestions of shared genetic variance.

8.3. General Limitations

The overall findings of these Chapters need to be considered in the context of several limitations relating to the methodological designs of the G1219 and ECHO studies. Caveats associated with the twin design and drawbacks of each specific study have been discussed in detail in other Chapters and are not repeated here. Instead several design-related artefacts which apply to all studies are presented here, including the definition and assessment of depression, the method of data collection and the recruitment and representativeness of these samples to the general population.

8.3.1. Definition and Assessment of Depression

The definitions of depression used in this thesis were based upon self-reported questionnaires assessed in non-clinical samples. Thus the phenotype under study, and to which the present results apply, is a continuous measure of normal variation rather than a diagnostic category. Although there is ample evidence that continuous definitions of depression vary on a continuum of severity with depressive disorder (Lewinsohn et al, 1998; Pickles et al, 2001; Roberts et al, 1995; Rueter et al, 1999) and moreover that there are few differences in the genetic and environmental aetiology of clinical phenotypes compared to those obtained from the normal range (e.g. Glowinski et al, 2003), the single dimension of depressed mood assessed in the current studies is still unlikely to reflect the complexity of diagnostic phenotypes. Thus high-scoring individuals in the current samples may not necsssarily approach clinically significant thresholds. Interpretations of the present findings should therefore be within the confines of depressed mood only, and any generalisations to depressive disorder should be made with caution.

A second note in relation to the depressive phenotype assessed in the current analyses is the validity of self-reported symptoms. This point is particularly pertinent to participants of the younger sample, whose level of cognitive and emotional development may impede their competency at completing and reporting on emotional symptoms. Yet in spite of the discrepant findings of poor inter-rater agreement between child and parent reports, there is counter evidence to show good concordance between child-reported depressive symptoms and clinical diagnoses (Rubio-Stipec et al., 1994). Moreover children aged 8 and above are likely to have acquired the level of language comprehension and reading, and the ability to recognise self and other perspectives on different emotions, needed to complete these questionnaires (Harrington, 1993). Participants of the ECHO study were also closely supervised by research assistants to help with reading and comprehension during the assessments.

In summary both the Mood and Feelings Questionnaire and the Children's Depression Inventory Questionnaire self-reported versions have good proven psychometric properties and were appropriate for the current studies (Costello & Angold, 1988; Costello et al, 1991; Kovacs, 1985). However to ensure the most accurate depiction of the depressive phenotype, future studies should consider multi-informant measures incorporating information from continuous and diagnostic tools.

8.3.2. Method of Data Collection

Data for the current analyses were collected from two population-based samples of twins and siblings. The sample sizes of both readily exceed what is normally seen in psychological studies. Whilst a large number of participants is undoubtedly a strength, particularly in terms of available statistical power, a major drawback is that such studies often have to rely on simpler and cruder measures for logistical and cost-related reasons. Thus the G1219 data was collected through postal means, restricting measures primarily

to questionnaires rather than detailed interviews, observational ratings or physiologically-based measures. A specific example of this was that zygosity was determined primarily through parental questionnaires of twin similarity rather than the preferred method of DNA genotyping. Whilst these restrictions applied less to the ECHO study, where participants completed a three hour assessment battery under the supervision of trained Psychology graduates, time restraints still prohibited the collection of more detailed measures for several of the studied variables. The impact that this limitation has on the validity of findings is likely to vary across the different sets of analyses conducted in this thesis and have been elaborated in more detail in each individual Chapter. However in general, any measurement error has been included within the non-shared environmental term, which may have been inflated at the expense of shared environmental effects.

8.3.3. Recruitment of Sample

An additional drawback associated with large sample sizes is that of recruitment, with particular issues of low response rates and subsequent attrition. This problem is clearly apparent in the G1219 sample, which had an initial response rate of between 20% to 47%, and subsequent response rates of 73% and 43% between Waves 1 and 2, and Waves 2 and 3 respectively. More worrying was that these response and attrition rates were significantly biased with a seemingly greater loss of families from socially disadvantaged backgrounds. Thus parental educational levels, which are an indicator of socio-economic status, were somewhat higher in the G1219 sample compared with a large nationally represented sample of parents (Meltzer et al, 2000). Moreover housing tenure and educational levels continued to predict attrition, such that adolescents from owner-occupied and more educated families were more likely to respond at subsequent time-points. Whilst a weighting system was generated and applied to all analyses to minimise the impact of this selectivity across time, it is important to recognise that the

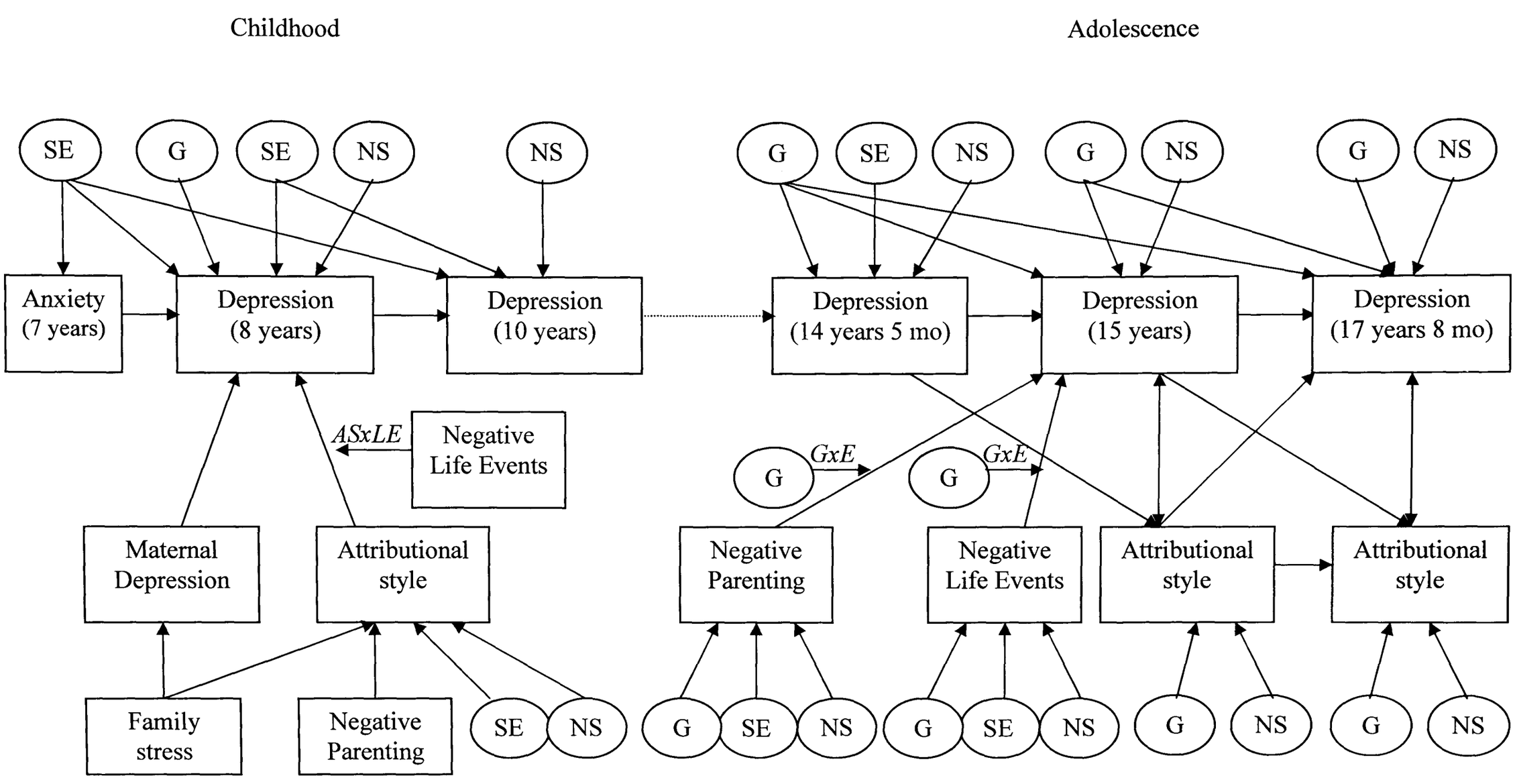
sample is still under-representative of extreme social conditions which may be of paramount importance in the development of depressive symptoms. One possible consequence of this, as discussed in Chapter 4 is an under-estimation of environmental effects, in spite of the weighting system. Genetic and environmental effects are specific to the population studied and any biases which may induce changes in the distribution of phenotypic scores will necessarily impact upon the findings.

A final note in relation to attrition rates was the increasing number of missing data across Waves of the study. This can be particularly problematic for analyses that rely on data from pairs of individuals, where data for one participant may be missing. However instead of omitting data for both members of the pair from the analyses, raw data modelling in Mx uses all information available to estimate the variance-covariance and mean structures, excluding only individuals with no valid data. Thus Mx adopts a 'missing at complete random' approach (Neale et al, 1999).

8.4. Interpretations and Implications

The aim of this thesis was to examine risk mechanisms which may underlie genetic, cognitive and psychosocial risks on depression symptoms and to address how the role of development may impact on the operation of these risk mechanisms. A summary of the research questions posed and the findings of each set have already been presented. The current section focuses on interpreting these results with respect to different pathways towards depression symptoms across childhood and adolescence. A summary of main results is presented in diagrammatic form in Figure 8.1.

Figure 8.1: A summary of main research findings



This model encapsulates the *main* findings across the study Chapters, with aims of illustrating how genetic, cognitive and psychosocial influences relate with one another to influence depression and how these may differ between childhood and adolescence. The model is conceptual rather than technical, that is, the elements are not strictly based on the notation of structural equation modelling. Nevertheless latent factors such as genetic (G), shared environment (SE) and non-shared environment (NS) are represented as circles and other measured variables as rectangles. The model is not exhaustive and does not cover all results but implicates only the most important pathways demonstrated. Additionally, to simplify the model, common genetic or environmental effects between measured variables were not represented but instead will be elaborated upon in the text to follow. Different aspects of this model form the discussion of three principle implications: developmental differences in aetiology; genetically and environmentally mediated pathways in adolescence; and psychosocial risk mechanisms in childhood, which are discussed in turn. It may be noted that unlike the study chapters, implications for adolescent depressive phenotypes are described first in the current Chapter. This is done so as to be consistent with adolescent conditions forming the main focus of this thesis (Section 2.5.2), with findings from the child sample acting as a developmental comparison, in which to view developmentally-related changes.

8.4.1. Developmental Differences in Aetiology

As can be seen from Figure 8.1, several differences in vulnerability factors and mechanisms occurring in childhood and in adolescence are present. Most notably there are differences in the extent to which genetic, shared and non-shared environmental influences contribute towards depressive symptoms and are involved in developmental continuity and change, all represented in the top half of the diagram. Additionally more specific differences in the mediation and moderation effects governing the inter-relationships between genetic, cognitive and psychosocial factors have also been found,

as depicted in the bottom half of the diagram. This section describes the general differences involving the role of latent genetic and environmental influences on depressive symptoms, whilst sections 8.4.2 and 8.4.3 elaborate on variations in specific pathways in adolescents and children respectively.

A profile of rather large genetic effects in early to middle childhood (3 to 7 years) followed by a period of attenuation from middle to late childhood (8 to 12 years), before increasing to a peak in adolescence (12 year onwards) has been demonstrated when extrapolating across cross-sectional comparisons of behavioural genetic studies of depressive symptoms in different age groups (see Section 2.2.2.2). In comparison shared environmental effects are smaller in early childhood, reach a maximal point at middle childhood and slowly decrease between late childhood and the onset of adolescence, where they subsequently diminish. Non-shared environmental effects are by contrast relatively large across most ages. Thus what emerges across the literature appears to be a developmentally-sensitive curve, characterising the changing magnitude of genetic and shared environmental effects. The current findings, which identified larger genetic effects in adolescence, compared to middle childhood are consistent with this pattern. Whilst there were modest genetic influences at age 8 of the child sample, this component fell at age 10. Instead, shared environmental effects steadily increased between ages 8 and 10 of the child sample. Non-shared environmental effects, which include measurement error, were substantial in both groups.

An interesting complement to these findings is the emergence of new genetic and environmental effects during certain time-points across development. Existing results have generally reported 'stable' genetic influences contributing to phenotypic continuity, and 'new' environmental variance effecting change (O'Connor et al, 1998b; Silberg et al, 1999), but there are two studies in addition to the current study deviating from this pattern. Specifically 'new' genetic as well as 'new' environmental effects

were found. What is notable across these findings was that all samples spanned age ranges which may involve age-related biological or cognitive milestones during crucial developmental transitions. Thus one study demonstrated age-specific genetic factors operating at 3 years and at 7 years (van der Valk et al, 2003), a period corresponding to the acquisition of new cognitive and emotional skills, such as the internalisation of actions into thoughts (Piaget, 1952) including language, theory of mind and executive function, all of which may influence a child's emotional regulation, and thus internalising symptoms. A second study found new genetic effects in a sample aged between 5 and 14 years emerging over a period of 3 years (Scourfield et al, 2003), where some of the sample may be entering the first stages of puberty. Finally in the current study, new genetic influences appeared at Wave 2 of the adolescent sample, where the mean age was 15 years. This age is roughly when increases in depressive symptoms are observed, particularly in females, and has been attributed to the transition to Tanner Stage III of puberty. Notably, this age range also witnesses developmental changes to the functioning of attributional style, which becomes fully operational during this period.

It is therefore plausible that developmentally-sensitive genes 'switched on' during critical periods of development are responsible for enacting new biological and cognitive challenges, which in turn have strong effects on depressive symptoms. New genetic effects in the current adolescent sample suggest that this may be one such period. However age-specific environmental effects demonstrated in this sample are also indicative of 'new' social challenges too.

In middle childhood, the converse can be argued such that new sources of shared and non-shared environmental effects are operational. Although there were some new genetic effects too, these did not contribute much towards continuity in symptoms. Instead the current findings demonstrate that shared environmental effects on depressive

symptoms were made up of 'stable' effects shared with early anxiety symptoms, and 'new' effects specific to depression at age 8. As with the adolescent sample, new non-shared environmental effects also emerged at each time-point. Whereas genetically-driven biological changes may characterise adolescent depression symptoms, similarly, social influences may be critical to stable emotional development in middle childhood.

These interpretations are tentative and clearly require a more detailed elucidation of genetic and shared environmental effects across development, but it is intriguing to speculate on processes underlying the pattern of genetic and environmental effects at different developmental stages. Possible candidate processes are discussed next.

8.4.2. Genetically and Environmentally Mediated Pathways in Adolescence

The current thesis examined two specific pathways through which increased genetic and non-shared environmental factors may influence depression symptoms in adolescence. The first involved the expression of genetic liability through interplay with environmental factors whilst the second addressed cognitive aspects of stress reactivity.

Accumulating evidence suggests that genetic and environmental effects on depression are not independent risk factors, but instead interact and correlate with one another to increase vulnerability to the phenotype. Specifically genetic risks may influence environmental risk exposure, gene-environment correlation. In the current study, genetic effects were demonstrated for a number of social factors including negative life events and maternal punitive discipline, in addition to correlations between maternal neuroticism and family chronic stressors with genetic liability during adolescence. More importantly, genetic effects on these risk variables overlap with those contributing towards depression symptoms suggesting that genetic vulnerability for the phenotype is expressed through exposure towards high-risk environments.

These effects may arise through passive, evocative and active processes (see Section 2.2.3.1). Thus correlations between genetic risks for depression and family chronic stress and maternal neuroticism may occur through passive processes. That is, depressed mothers and the rearing environments are reflective of genetic as well social risks to offspring. In comparison, genetic effects on maternal punitive discipline may represent an evocative process, such that genetically mediated traits of the adolescent, elicit certain reactions from his/her parents. Finally, genetic contributions to negative life events may be an example of active gene-environment correlation, whereby genetic propensities influence the creation and selection of negative stressors through life choices that may increase or decrease the likelihood of such events.

Genetic effects may also increase susceptibility towards certain environmental risks (gene-environment interaction). Although there have been a large number of recent articles dedicated to the examination of interactions (e.g. Eley et al, 2004b, Silberg et al, 2001), many have neglected to recognise that their results can also reflect correlations between genes and environments. In other words, the presence of gene-environment correlation may confound findings of gene-environment interaction. What was novel about the current results was that interaction effects between environmental risk factors and genetic risks were found even after gene-environment correlations were controlled for, increasing the validity of interaction effects. These results further emphasise that gene-environment correlations and interactions do not operate in a vacuum but instead co-occur dynamically. Thus both negative life events and maternal punitive discipline are simultaneously influenced by genetic effects, as well as interacting with genetic risks to increase vulnerability to depressive symptoms.

Genetic variance on depression symptoms increased across levels of severity of environmental stress, a finding which is consistent with other studies of gene-environment interaction (Silberg et al, 2001; Eaves et al, 2003) and with suggestions

that individual differences may be enhanced during periods of social change (Caspi & Moffitt, 1991). Adolescents with higher genetic liability, who are additionally exposed to a double disadvantage of correlated environmental adversity, may be more susceptible towards the risk effects of these environments. Such findings are consistent with proposals of diathesis-stress theories of depression, where the occurrence of an environmental stressor elicits a latent predisposition, which enhances risks towards depressive symptoms. As such genetic effects may plausibly act upon core processes of stress reactivity. These findings pave the way for examining a second route through which genetic and environmental effects on depression are mediated.

Negative attributional style is a well-known cognitive factor which influences responses towards negative experiences, and predisposes towards depression symptoms. In Chapter 6, several sets of analyses to determine whether attributional style was a suitable marker of genetic and environmental effects on depression symptoms was conducted. First moderate genetic and substantial non-shared environmental effects on attributional style were found, implying that this cognitive factor is more than just a learned trait but is also heritable. Second common genetic and common non-shared environmental influences between the two measures were demonstrated. These shared factors also accounted for roughly equal proportions of the observed correlation in mid-adolescence (mean age: 15 years). However by late-adolescence (mean age: 17 years 8 months), the genetic links between attributional style and depression had increased, as well as the extent to which it explained their observed correlation, rising from 31% to 66%. In contrast, the overlap between non-shared environmental effects was comparable at the two time-points, as was its contribution towards the correlation (44% and 34%). As discussed in the next section, a similar sized correlation was reported between attributional style and depression in the child sample, but this association was accounted for largely by common non-shared environmental effects.

One interpretation of these results is that attributional style mediates distal genetic and environmental risks on depressive symptoms in adolescence. Thus negative attributions could constitute a cognitive manifestation of a genetically mediated predisposition towards depression (e.g. emotional reactivity or neuroticism) (Hankin & Abramson, 2001; Murray et al, 2001). In addition, attributional style could reflect incremental effects of distal environmental factors involved in depression, such as negative events or parental practices. Consistent with the role of a mediator of distal genetic and environmental effects, attributional style was also found to predict depressive symptoms across time, even after controlling for concurrent and consequential effects. Contrary to expectations, this 'causal' effect did not interact with life events to influence symptoms. Thus although attributional style may mediate genetic and social risks on depression, these vulnerability effects were not elicited through interaction with the environment.

In summary genetic effects may be expressed in adolescence through an increased exposure towards environmental risk factors, mediated through passive, evocative and active processes; an increased sensitivity towards such risks mediated through stress-reactivity; and more tentatively, through the development of a negative attributions.

8.4.3. Psychosocial Risk Mechanisms in Childhood

In comparison to the adolescent findings, genetic effects on depression symptom measures collected in the child sample were minimal. Instead, a predominant role for environmental influences was implicated. Two approaches were utilised to gain insight into candidates representing these environmental effects. The first examined attributional style as a possible marker of environmental effects in childhood, whereas the second aimed to unpick the sources of environmental variance in depressive symptoms and attributional style, by identifying specific pathways through which psychosocial factors influenced these variables.

Attributional style may develop in childhood through negative events, social learning and feedback, parental depression and negative parenting practices (see Section 2.2.3). Consistent with depictions of social mediation, results in the current study indicated that attributional style assessed in middle childhood is largely the product of environmental contributions. Whilst non-shared environmental factors were substantial, shared environmental effects fell short of significance. In terms of the phenotypic association between attributional style and depression symptoms, common non-shared environmental influences were implicated. Furthermore these explained around half of the observed correlation. Given more power, it was expected that common shared environmental effects between attributional style and depressive symptoms would be present too, and would contribute towards the phenotypic correlation. In general the results were suggestive that this cognitive factor is reflective of environmental vulnerability on childhood depression symptoms.

The question of which specific environmental influences were reflected in the attributional style and depression relationship was targeted in a second set of analyses. Results supported two interesting pathways. The first showed that attributional style may mediate the risk effects of living in a step or single-parent family and maternal punitive discipline on depression symptoms. Second, the occurrence of negative life events increased the effects of attributional style on depressive symptoms. Together these results are suggestive that the association between attributional style and depression in childhood reflects the mediation of distal social vulnerability and the influence of proximal social stressors in eliciting these vulnerabilities.

A final pathway also thought to reflect environmentally mediated risks on child depression symptoms independent of attributional style was maternal depression. This also mediated vulnerability associated with living in a step- or single-parent family. However it is likely that the effects of maternal depression on child depressive outcome

involve complex relationships with other factors, such as negative parent-child relations or family chronic stress, which were not assessed in the current study.

In summary, a likely social route to depression symptoms involved attributional style, which mediated distal vulnerabilities of the family environment. Moreover, the effects of this pathway can be increased significantly by the presence of stressful life events.

8.4.4. Concluding Remarks

A principle implication of these results is the difference in the relative *size* of genetic and environmental effects on depressive symptoms in childhood and in adolescence. Examining specific pathways also highlights possible differences in pathways underlying genetic and environmental effects between developmental stages, with the most marked difference being attributional style, which mediates genetic vulnerability in adolescence but social risks in childhood. Whilst these changes are likely to reflect a continuous trajectory of development, they underscore the role of developmentally-sensitive factors. These may include genes which come online during adolescence, and which might incur neural and in turn cognitive changes to alter the functioning of attributional style, or age-normative stressors, which impact upon the initial acquisition of negative cognitions. In summary, the inter-relationships between genetic, cognitive and psychosocial factors on the aetiology of depression are not static but instead change in a dynamic fashion across developmental stages.

8.5. Future Directions

In addition to the usual maxim of replicating the results obtained in this thesis, future research can be divided into three themes. The first is to examine the intricacies of the pathways through which genetic predispositions on depression symptoms may be expressed. The current findings implicate gene-environment correlation and gene-

environment interactions, but understanding how these indirect effects are mediated is a critical next step. The search for mediators can be pioneered from many different levels, from bottom-up approaches, such as candidate genes and the neurobiological systems which they regulate (Caspi et al., 2003; Eley et al., 2004); to more intermediate processes such as brain function and structure (Hariri et al., 2002); and finally to more top-down approaches, such as vulnerability associated with personality or cognitive factors, as demonstrated in the current studies. Whilst appreciating this broad spectrum of approaches, it is important to also acknowledge the links between the different mediators and whether these reflect the same vulnerability.

A second strand of research is the identification of putative sources of environmental effects and understanding the nature of these effects and the mechanisms by which they operate. The first challenge lies in developing new methodological and analytical techniques of assessing the impact of the environment whilst controlling for confounding genetic effects (Rutter et al, 2001). Although there have been attempts to do this within the twin design (e.g. Kim-Cohen et al, 2005), the validity of these approaches has been queried (Purcell & Koenen, 2005). As discussed in Chapter 7, understanding the *nature* of mediating mechanisms through which a risk factor influences an outcome, will necessarily involve delineating (and controlling for) its *origins*. Other challenges include analytically differentiating shared from non-shared environmental sources; distinguishing stressors as predisposing, vulnerability or protective; and examining other pathways that involve mediation and moderation effects, which govern the inter-relationships among variables.

The final strand of research is to consider genetic and environmental risk mechanisms in the context of development. In doing so, it is of paramount importance that 'development' is not regarded as inter-changeable with chronological age (Rutter, 2003). Instead a developmental approach should be sensitive to any new biological,

cognitive or social changes that are normative to transitions between stages of development. Thus genetic risk mechanisms demonstrated post-puberty may not necessarily concur with those identified in pre-pubertal children. Similarly, the impact of particular environmental stimuli, such as those arising in the family environment may become less important as children reach adolescence. Understanding the aetiology of depression symptoms from a holistic approach extends beyond establishing links between different disciplinary approaches, but to appreciating the moderating role of development.

8.6. Clinical Implications

Studies of the current thesis have sought explanations of the aetiology of depression symptoms from the perspectives of genetic and environmental causes, and cognitive and psychosocial pathways. Their findings have readily reinforced the importance of each of these levels of vulnerability in the development of depressive outcomes. An important next step is to translate the implications these have for the treatment and prevention of these conditions, which may operate from an early age and potentially continue into adulthood. Although this thesis is relatively restricted in terms of *direct* implications for the clinical practitioner, given the non-clinical nature of the sample and the non-diagnostic definitions of depression used, it is important to recognise that these implications may also be considered on a broader scale, to helping individuals who may be manifesting more moderate forms of these conditions in the general community.

The stereotypical view of genetic explanations of behavioural phenotypes, particularly those involving aspects of emotional functioning includes apprehension, a fear of genetic determinism and the end of free will. It is perhaps paradoxical that the preferred view that environmental events cause depression is also plagued with the same degree of uncontrollability over the manifestation of emotional symptoms. However findings

from the current thesis may counter some of the arguments of genetic and environmental determinism, by demonstrating that the effects of these factors are not direct but instead act through an intermediate level of negative cognitions. As cognitive biases may be re-structured and modified, these findings offer an opportunity to re-assert personal control over the development of depressive conditions. Furthermore, given findings of an interlocking relationship between attributional style and depression, targeting this cognitive level of vulnerability may also help to break the vicious cycle that often characterises this mood condition.

Cognitive-behavioural therapy interventions aimed at ameliorating cognitive biases have been effective in improving symptoms and reducing the risk of relapse in depressed adolescents (Harrington, Whittaker, Shoebridge & Campbell, 1998). There is also preliminary evidence that such interventions can *prevent* initial onsets of depression as well (DeRubeis, Seligman, Schulman, Reivich & Hallon, 1998). Thus primary prevention efforts aimed at building positive cognitive styles in children who are suspected of possessing a genetic propensity or at high social risk for depressive conditions (e.g. children of depressed parents), can equip children with more effective coping strategies towards stress. Such programs can involve a simultaneous education of parents on how they can act as role-models or provide feedback on more benign inferences for academic or social stressors faced by their offspring. Alternatively, classroom interventions through school-based programs can reach out to individuals from unselected populations (Shattè, Gillham & Reivich, 2000).

Although these initiatives show some promise for combating the distally mediated risk effects associated with nature and nurture, randomised trials of longer periods are still needed to determine more precise success rates. A further priority raised by a recent article detailing recommendations for future collaborative research indicated the

urgency of developing age-appropriate psychotherapeutic interventions for children of different ages and levels of cognitive and emotional development (Costello et al, 2002).

8.7. Conclusions

The beginning of the new millennium has ushered in new research priorities in the area of child mood disorders, amongst which is an explicit endorsement of multidisciplinary research (Costello et al, 2002; Davidson et al, 2002). Bearing witness to this growing priority is the increased number of multifactorial conceptual models used to explain the aetiology of emotional phenotypes (e.g. Goodman & Gotlib, 1999; Hankin et al, 2001; Rapee et al, 2001). Such models have attempted to understand the interaction between several different domains of vulnerability factor and the developmentally-sensitive pathways through which their risks are expressed and manifested. In keeping with this theme, the current thesis has aimed to present one possible model of the development of depressive symptoms in children and adolescents. This has been based on results from the empirical testing of links between genetic, environmental, cognitive and psychosocial factors. Whilst there is a clear need for future studies to replicate and clarify certain aspects of the model, and undoubtedly the model will undergo many changes as a result, it is hoped that the current model can contribute towards the formulation of new hypotheses and channel research efforts.

Appendix A: Measures

A.1. Short Mood and Feelings Questionnaire (Angold et al, 1995)

How often have you felt or acted in this way over the past two weeks?

1. I felt miserable or unhappy
2. I didn't enjoy anything
3. I just felt so tired I just sat around and did nothing
4. I was very restless
5. I felt I was no good anymore
6. I cried a lot
7. I found it hard to think properly or concentrate
8. I hated myself
9. I was a bad person
10. I felt lonely
11. I thought that nobody really loved me
12. I thought I could never be as good as others
13. I did everything wrong

Rating: (Never, Sometimes, Often, Always)

A.2. Parental Educational Level and Housing Tenure

Education: Please mark a cross for all that apply:

- No qualifications
- CSE
- 'O' level of GCSE
- 'A' level, 'AS' level, 'S' level
- Higher National Certificate (HNC)
- Higher National Diploma (HND)
- University degree (e.g. BA, BSc)
- Postgraduate degree (e.g. Masters, PhD)
- Other: Please specify

Housing: Please put a cross in the one box that best describes your present housing:

- Owned
- Rented
- Housing Association / Council
- Living in parent's home
- Other: Please specify

A.3. Eysenck Personality Questionnaire Neuroticism Scale (Eysenck, Eysenck, & Barrett, 1985)

1. Does your mood often go up and down?
2. Do you ever feel 'just miserable' for no reason?
3. Would you call yourself a nervous person?
4. Are you an irritable person?
5. Are your feelings easily hurt?
6. Do you often feel 'fed-up'?
7. Are you a worrier?
8. Would you call yourself tense or 'highly-strung'?
9. Do you worry too long after an embarrassing experience?
10. Do you often suffer from 'nerves'?
11. Do you often feel lonely?
12. Are you often troubled about feelings of guilt?

Rating: Yes / No

A.4. Social Problems Questionnaire (Corney, 1988)

Section 1: Housing

1. How satisfied are you with your present housing situation?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

2. Do you have problems with your neighbours?

Rating: No problems / Slight problems / Marked problems / Severe problems

Section 2: Work

3a. How satisfied are you with your present job?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

3b. Do you have problems getting on with any of the people at your work?

Rating: No problems / Slight problems / Marked problems / Severe problems

If you have a job and look after your home:

4. How satisfied are you with working and running a home?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

If you do not have a paid job:

5. How satisfied are you with not having a paid job?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

Section 3: Finances

6. Do you have any difficulties in meeting bills and other financial commitments?

Rating: No difficulties / Slight difficulties / Marked difficulties / Severe difficulties

7. How satisfied are you with your financial position?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

Section 4: Relationships

8. What is your marital status?

Rating: Single / Married / Living with partner / Widowed / Separated/divorced

If you are married or have a long term partner:

9a. How satisfied in general are you with your relationship?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

9b. In the last 6 months, have you been so dissatisfied that you have considered separating from your partner?

Rating: No / Sometimes / Often / Yes, planned or recent separation

For all:

10. Are there any problems with your sex life?

Rating: No problems / Slight problems / Marked problems / Severe problems

If you have children under 18 years old:

11a. How many children are there living in your household?

11b. Do you have any problems with your children at home or school?

Rating: No problems / Slight problems / Marked problems / Severe problems

11c. How satisfied do you feel with your relationship with the children?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

If you live with other adults in the house:

12a. Do you have any problems with these other adults (including difficulties sharing household tasks)?

Rating: No difficulties / Slight difficulties / Marked difficulties / Severe difficulties

12b. How satisfied are you with this arrangement?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

If you are single:

13. How satisfied are you with not having a partner?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

Section 5: Social Life

14. How satisfied are you with your social life?

Rating: Satisfied / Slightly dissatisfied / Markedly dissatisfied / Severely dissatisfied

15. Do you feel alone?

Rating: Never / Sometimes / Often / Always

16. Do you have any problems getting on with someone not living in your home who is important to you (e.g. a relative or a friend)?

Rating: No problems / Slight problems / Marked problems / Severe problems

A.5. List of Threatening Experiences Questionnaire (Brugha, Bebbington, Tennant, & Hurry, 1985)

The following questions are about events or problems that may have happened to you during the past 6 months which might have caused you distress. Please answer each item by putting a cross in either the 'yes' or 'no' box.

1. you yourself suffered a serious illness, injury or an assault
2. a serious illness, injury or assault happened to a close relative
3. your parent, child or spouse died
4. a close family friend or another relative (aunt, cousin, grandparent) died
5. you had a separation due to marital difficulties
6. you broke off a steady relationship
7. you had a serious problem with a close friend, neighbour or relative
8. you became unemployed or you were seeking work unsuccessfully for more than one month
9. you were sacked from your job
10. you had a major financial crisis
11. you had problems with the police and a court appearance
12. something you valued was lost or stolen

Rating: Yes / No

A.6. Children's Attributional Style Questionnaire (Kaslow & Nolen-Hoeksema, 1991)

For each situation, there are also two possible reasons for why the situation might have happened. Chose the most likely reason to explain why the situation happened to you.

1. You get an "A" on a test
    A. I am smart
    B. I am good in the subject that the test was in
2. Some people that you know say that they do not like you
    A. Once in a while people are mean to me
    B. Once in a while I am mean to other people
3. A good friend tells you that he hates you
    A. My friend was in a bad mood that day
    B. I wasn't nice to my friend that day
4. A person steals money from you
    A. That person is not honest
    B. Many people are not honest
5. Your parents tell you something that you make is very good
    A. I am good at making some things
    B. My parents like some things I make
6. You break a glass
    A. I am not careful enough
    B. Sometimes I am not careful enough
7. You do a project with a group of others and it turns out badly
    A. I don't work well with people in that particular group
    B. I never work well with groups
8. You make a new friend
    A. I am a nice person
    B. The people that I meet are nice
9. You have been getting along well with your family
    A. I am usually easy to get along with when I am with my family
    B. Once in a while I am easy to get along with when I am with my family
10. You get a bad mark in school
    A. I am not a good student
    B. Teachers give hard tests

11. You walk into a door and you get a bloody nose

A. I wasn't looking where I was going

B. I have been careless lately

12. You have a messy room

A. I did not clean my room that day

B. I usually do not clean my room

13. Your mother makes you your favourite dinner

A. There are a few things that my mother will do to please me

B. My mother usually likes to please me

14. A team that you are on loses a game

A. The team members don't help each other when they play together

B. That day the team members didn't help each other

15. You do not get your chores done at home

A. I was lazy that day

B. Many days I am lazy

16. You go to an amusement park and have a good time

A. I usually enjoy myself at amusement parks

B. I usually enjoy myself in many activities

17. You go to a friend's party and you have fun

A. Your friend usually gives good parties

B. Your friend gave a good party that day

18. You have a substitute teacher and she likes you

A. I was well behaved during class that day

B. I am almost always well behaved during class

19. You make your friends happy

A. I am usually a fun person to be with

B. Sometimes I am a fun person to be with

20. You put a hard puzzle together

A. I am good at putting puzzles together

B. I am good at doing many things

21. You try out for a sports team and do not make it

A. I am not good at sports

B. The others who tried out were very good at sports

22. You fail a test

A. All tests are hard

B. Only some tests are hard

23. You score a goal in a football game

A. I got the shot just right

B. The goalkeeper was easy to beat

24. You do the best in your class on a paper

A. The others in my class did not work hard on their papers

B. I worked hard on the paper

Rating: A or B

A.7. Life Event Scale for Adolescents (Coddington, 1984)

Here is a list of events that might have happened to you recently. Please put a cross in the box if the event has happened to you in the past year.

1. Outstanding personal achievement (special prize)
2. Finding an adult that really respects you
3. Stopping the use of drugs
4. Becoming involved with drugs
5. Death of a close friend
6. Being hospitalised for illness or injury
7. Being sent away from home
8. Deciding to leave home
9. Becoming an adult member of a church
10. Failing to achieve something you really wanted
11. Appearance in juvenile court
12. Recognition for excelling in a sport or other activity
13. End of a problem between you and your parents
14. Start of a new problem between you and your parents
15. Suspension from school
16. Failing end of year exams
17. Move to a new school district
18. Beginning the first year of GCSEs
19. Being told you are very attractive by a friend
20. Mother beginning to work outside the home
21. A new adult moving into your home
22. Change in father's job so he has less time home
23. End of a problem between your parents
24. Start of a new problem between your parents
25. Major decrease in your parents' income
26. Major increase in your parent' income
27. Loss of a job by your father or mother
28. Hospitalisation of a brother or sister
29. Birth of a brother or sister
30. Remarriage of a parent to a stepparent
31. Hospitalisation of a parent

32. The death of a grandparent
33. Marital separation of your parents
34. Divorce of your parents
35. The death of a brother or sister
36. The death of a parent
37. Getting married
38. Getting pregnant or fathering a pregnancy
39. Getting your first permanent job
40. Getting your first summer job
41. Being responsible for a road accident
42. Getting your first driver's license
43. Being invited to join a social organisation
44. Being accepted at the university of your choice
45. Completing sixth form
46. Being told to break up with a boy/girl friend
47. Finding a new boy/girl friend
48. Being invited by a friend to break the law
49. Breaking up with a boy/girl friend
50. Going out with someone for the first time in your life

A.8. Negative Sanctions and Communication About Discipline sub-scales (O'Connor et al, 2001)

How common is it for your MUM to:

1. Talk to you about something you did wrong, to give a reason of why something you did was wrong?
2. Yell at you about something you did wrong?
3. Take away privileges from you for something you did wrong? (e.g. No TV, no dessert etc)
4. Make fun of you or put you down when the two of you argue?
5. Apologise after an argument turned out wrong?
6. Compromise during a disagreement or argument? ("compromise" means both giving a little)
7. Tell you to do something "because I said so"?
8. Talk over with you a decision that concerns you? (e.g. moving house, decorating your room)
9. See that you obey rules?

Rating: Very uncommon, Uncommon, Somewhat Common, Common, Very Common

A.9. Parent-reported Child Anxiety items (Goodman, 1997)

Here are some descriptions of children. Please tell us if you think each statement is certainly true, somewhat true or not true.

1. Many fears, easily scared
2. Many worries, often seems worried
3. Often unhappy, downhearted or tearful
4. Nervous or clingy in new situations, easily loses confidence
5. Often complains of stomach aches, headaches or sickness
6. Anxious that bad things will happen
7. Seems keyed up, on edge or tense
8. Is afraid of small closed spaces, heights, water, or the dark
9. Is afraid of animals or insects (like dogs, spiders, snakes, or insects)
10. Is afraid of medical procedures or going to see the doctor/dentist
11. Is afraid in social situations
12. Strongly refuses or resists sleeping alone
13. Is often extremely upset or distressed when parent leaves
14. Asks for reassurance that s/he is OK
15. Tends to blame him/herself
16. Often makes comments critical of him/herself
17. Has low self-confidence
18. Doesn't enjoy him/herself
19. Complains or whines a lot
20. Tends to be shy or timid
21. Takes a long time to warm to strangers

Rating: certainly true, somewhat true or not true

A.10. Parental marital status and living arrangements

1. What is your relationship to your twins?
   - Birth mother
   - Stepmother
   - Foster mother
   - Natural/biological father
   - Stepfather
   - Foster father
   - Grandmother
   - Grandfather
   - Other (please describe)
2. Do you currently live with a partner/spouse?
   - Yes
   - No
3. If Yes to (2), And what is his/her relationship to the twins?
   - Birth mother
   - Stepmother
   - Foster mother
   - Natural/biological father
   - Stepfather
   - Foster father
   - Grandmother
   - Grandfather
   - Other (please describe)
4. Please can you tell us your marital status at this present time?
   - married to the natural parent of the twins
   - married to someone else
   - cohabiting with the parent of twins
   - cohabiting with someone else
   - divorced
   - separated
   - widowed
   - unmarried

A.11. SES (Pike et al, in press)

What educational qualifications do you (or your partner) have:

- No qualifications
- CSE (Grade 2, 3, 4, 5) or GCSE (D, E, F, G)
- CSE (Grade 1) or GCSE (A, B, C)
- 'A' level, 'S' level
- Higher National Certificate (HNC)
- Higher National Diploma (HND)
- Undergraduate degree
- Postgraduate qualification (e.g. Masters, PhD)
- Other: Please describe

Do you currently have a job?

- Yes
- No
- Staying at home to look after the children

Of the following, which best describes you (or your partner) at work:

- Manager
- Employee
- Foreman
- Apprentice
- Self-employed – with employees
- Self-emplyed – with no employees

Pleas tell us about the twins' older brothers and sisters:

Child's name / Date of birth / Boy or Girl

Does this child have the same parents as the twins?

About you: What is your relationship to your twins? (see Appendix A.10)

Date of birth

A.12. **Parental Punitive Discipline** (Deater-Deckard et al, 1998)

Below are descriptions of some things parents do to help their children behave well. When answering the following questions, please think about the twins individually because sometimes different children need a different approach.

1. Do you talk about good and bad behaviour, explain why or reason with the ELDER twin? How often do you do this?
2. Do you do this more or less often with the YOUNGER twin?
3. Do you ever restrain or smack the ELDER twin? How often do you do this?
4. Do you do this more or less often with the YOUNGER twin?
5. Do you ever send the ELDER twin to her/his room or withdraw privileges? How often do you do this?
6. Do you do this more or less often with the YOUNGER twin?
7. Do you ever raise your voice or shout at the ELDER twin? How often do you do this?
8. Do you do this more or less often with the YOUNGER twin?
9. Do you ever ignore the ELDER twin when he/she is misbehaving? How often do you do this?
10. Do you do this more or less often with the YOUNGER twin?
11. Do you use praise and rewards for good behaviour with the ELDER twin? How often do you do this?
12. Do you do this more or less often with the YOUNGER twin?

Rating:

ELDER TWIN: Never, Rarely (once a month or less), Sometimes (Weekly or so), Often (more than once a week))

YOUNGER TWIN: Less, Same, More

A.13. **Parent depression index** (McGuffin et al, 1986)

1. Have you ever had problems with nerves at any time in the past?
2. Have you ever been referred to a psychiatrist?
3. Have you ever seen your own doctor about difficulties with nerves, tension or depression?
4. Have you ever consulted some other professional person about emotional problems?
5. Have you had more than one spell when you have been seriously depressed or anxious or suffered in some other way with your nerves?

Rating: Yes / No

A.14. Life Event Scale for Children (Coddington, 1984)

1. Has your child been hospitalised for illness or injury in the past year?
2. Has a close friend of your child died over the past year?
3. Has your child experienced the remarriage of a parent to a step-parent in the past year?
4. Has your child experienced the hospitalisation of a parent in the past year?
5. Has your child experienced the birth of a brother or sister over the past year?
6. Has your child experienced the death of a grandparent in the past year?
7. Has your child experienced the marital separation of parents in the past year?
8. Has your child experienced the divorce of parents in the past year?
9. Has your child experienced the death of a brother or sister in the past year?
10. Has your child experienced the death of a parent in the past year?
11. Has your child had an outstanding personal achievement (special prize) over the past year?

Rating: Yes / No

A.15. Children's Depression Index (Kovacs, 1981)

Put a tick next to the sentence that describes you best.

1. I am sad once in a while
   I am sad many times
   I am sad all the time
2. Nothing will ever work out for me
   I am not sure if things will work out for me
   Things will work out for me O.K.
3. I do most things O.K.
   I do many things wrong
   I do everything wrong
4. I have fun in many things
   I have fun in some things
   Nothing is fun at all
5. I am bad all the time
   I am bad many times
   I am bad once in a while
6. I think about bad things happening to me once in a while
   I worry that bad things will happen to me
   I am sure that terrible things will happen to me
7. I hate myself
   I do not like myself
   I like myself
8. All bad things are my fault
   Many bad things are my fault
   Bad things are not usually my fault
9. I feel like crying every day
   I feel like crying many days
   I feel like crying once in a while
10. Things bother me all the time
    Things bother me many times
    Things bother me once in a while
11. I like being with people
    I do not like being with people many times

I do not want to be with people at all

12. I cannot make up my mind about things

    It is hard to make up my mind about things

    I make up my mind about things easily

13. I look O.K.

    There are some bad things about my looks

    I look ugly

14. I have to push myself all the time to do my school work

    I have to push myself many times to do my school work

    Doing schoolwork is no big problem

15. I have trouble sleeping at night

    I have trouble sleeping many nights

    I sleep pretty well

16. I am tired once in a while

    I am tired many times

    I am tired all the time

17. Most days I do not feel like eating

    Many days I do not feel like eating

    I eat pretty well

18. I do not worry about aches and pains

    I worry about aches and pains many times

    I worry about aches and pains all the times

19. I do not feel alone

    I feel alone many times

    I feel alone all the time

20. I never have fun at school

    I have fun at school only once in a while

    I have fun at school many times

21. I have plenty of friends

    I have some friends here but I wish I had more

    I do not have many friends

22. My school work is all right

    My school work is not as good as before

    I do very badly in subjects I used to be good in

23. I can never be as good as other young people

I can be as good as other young people if I want to

I am just as good as other young people

24. Nobody really loves me

I am not sure if anybody really loves me

I am sure that somebody loves me

25. I usually do what I am told

I do not do what I am told most times

I never do what I am told

26. I get along with people

I get into fights many times

I get into fights all the time

Appendix B: Mx Scripts

B.1. Saturated Models and Descriptive Statistics

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! Mx saturated script for estimating the standard deviations (variance), correlations
! (covariances) and means for one variable across 8 zygosity groups in G1219
! A weight to account for possible response/attrition biases in G1219 is included
! Sub-models to test for group differences in means and covariances
! Models 1a and 1b tests mean differences between males and females
! Models 2a and 2b tests mean differences between zygosity groups
! Model 3 tests differences in within-pair covariances between DZ and FS pairs
! Model 4 tests phenotypic correlations between variables for whole sample

#Define nvar 2
G1: MZM twin pairs
Data NINPUT_VARS=20 NGROUPS = 8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 1.00 /
SELECT t1dep1 t1dep2 wgt1 ;
Definition wgt1 /
Begin Matrices;
R Stan nvar nvar        Free        ! Twin Correlation
S Diag nvar nvar        Free        ! Standard Deviation of Twin1 score and Twin2 score
M Full 1 nvar           Free        ! Mean of Twin1 and Twin2
W Full 1 1                          ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .3 R 2 1
Start 5 S 1 1 - S 2 2
Start 5 M 1 1 - M 1 2
Sp W -1
Weights W /
End

G2: MZF twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 3.00 /
SELECT t1dep1 t1dep2 wgt1 ;
Definition wgt1 /
Begin Matrices;
R Stan nvar nvar        Free        ! Twin Correlation
S Diag nvar nvar        Free        ! Standard Deviation of Twin1 score and Twin2 score
M Full 1 nvar           Free        ! Mean of Twin1 and Twin2
W Full 1 1                          ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .4 R 2 1
```

```
Start 7 S 1 1 - S 2 2
Start 7 M 1 1 - M 1 2
Sp W -1
Weights W /
End

G3:  DZM twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 2.00 /
SELECT t1dep1 t1dep2 wgt1 ;
Definition wgt1 /
Begin Matrices;
R Stan nvar nvar        Free        ! Twin Correlation
S Diag nvar nvar        Free        ! Standard Deviation of Twin1 score and Twin2 score
M Full 1 nvar           Free        ! Mean of Twin1 and Twin2
W Full 1 1                          ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .3 R 2 1
Start 5 S 1 1 - S 2 2
Start 5 M 1 1 - M 1 2
Sp W -1
Weights W /
End

G4:  DZF twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 4.00 /
SELECT t1dep1 t1dep2 wgt1 ;
Definition wgt1 /
Begin Matrices;
R Stan nvar nvar        Free        ! Twin Correlation
S Diag nvar nvar        Free        ! Standard Deviation of Twin1 score and Twin2 score
M Full 1 nvar           Free        ! Mean of Twin1 and Twin2
W Full 1 1                          ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .5 R 2 1
Start 7 S 1 1 - S 2 2
Start 7 M 1 1 - M 1 2
Sp W -1
Weights W /
End

G5:  DZO twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
```

```
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 5.00 /
SELECT t1dep1 t1dep2 wgt1 ;
Definition wgt1 /
Begin Matrices;
R Stan nvar nvar        Free        ! Twin Correlation
S Diag nvar nvar        Free        ! Standard Deviation of Twin1 score and Twin2 score
M Full 1 nvar           Free        ! Mean of Twin1 and Twin2
W Full 1 1                          ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .1 R 2 1
Start 5 S 1 1
Start 7 S 2 2
Start 5 M 1 1
Start 7 M 1 2
Sp W -1
Weights W /
End

G6:  MM Sib pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 6.00 /
SELECT t1dep1 t1dep2 wgt1 ;
Definition wgt1 /
Begin Matrices;
R Stan nvar nvar        Free        ! Twin Correlation
S Diag nvar nvar        Free        ! Standard Deviation of Twin1 score and Twin2 score
M Full 1 nvar           Free        ! Mean of Twin1 and Twin2
W Full 1 1                          ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .3 R 2 1
Start 5 S 1 1 - S 2 2
Start 5 M 1 1 - M 1 2
Sp W -1
Weights W /
End

G7:  FF Sib pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 7.00 /
SELECT t1dep1 t1dep2 wgt1 ;
Definition wgt1 /
Begin Matrices;
```

```
R Stan nvar nvar        Free        ! Twin Correlation
S Diag nvar nvar        Free        ! Standard Deviation of Twin1 score and Twin2 score
M Full 1 nvar           Free        ! Mean of Twin1 and Twin2
W Full 1 1                          ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .4 R 2 1
Start 7 S 1 1 - S 2 2
Start 7 M 1 1 - M 1 2
Sp W -1
Weights W /
End

G8:  OS sib pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 8.00 /
SELECT t1dep1 t1dep2 wgt1 ;
Definition wgt1 /
Begin Matrices;
R Stan nvar nvar        Free        ! Twin Correlation
S Diag nvar nvar        Free        ! Standard Deviation of Twin1 score and Twin2 score
M Full 1 nvar           Free        ! Mean of Twin1 and Twin2
W Full 1 1                          ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .2 R 2 1
Start 5 S 1 1
Start 7 S 2 2
Start 5 M 1 1
Start 7 M 1 2
Sp W -1
Weights W /
Options multiple
!Options multiple issat                 ! Uncomment when testing sub-model 3
End

Save grpdiff.mxs
Get grpdiff.mxs

! Model 1a: Estimate two means: one for males and one for females
EQ M 1 1 1 M 1 1 2 M 3 1 1 M 3 1 2 M 5 1 1 M 6 1 1 M 6 1 2 M 8 1 1  ! Male mean
EQ M 2 1 1 M 2 1 2 M 4 1 1 M 4 1 2 M 5 1 2 M 7 1 1 M 7 1 2 M 8 1 2  ! Female mean
Options multiple issat          ! Use when comparing models 1a and 1b
End

! Model 1b: Equate the means for males and females
EQ M 1 1 1 M 1 1 2 M 3 1 1 M 3 1 2 M 5 1 1 M 6 1 1 M 6 1 2 M 8 1 1 M 2 1 1 M 2 1 2 M 4 1 1
M 4 1 2 M 5 1 2 M 7 1 1 M 7 1 2 M 8 1 2                         ! One mean for all
End
```

```
! Model 2a: Estimate zyg-specific means for males (MZM, DZM, FSM) and zyg-specific means
for females (MZF, DZF, FSF)
EQ M 1 1 1 M 1 1 2              ! MZ males mean
EQ M 3 1 1 M 3 1 2 M 5 1 1      ! DZ males mean
EQ M 6 1 1 M 6 1 2 M 8 1 1      ! FS males mean
EQ M 2 1 1 M 2 1 2              ! MZ females mean
EQ M 4 1 1 M 4 1 2 M 5 1 2      ! DZ females mean
EQ M 7 1 1 M 7 1 2 M 8 1 2      ! FS females mean
Options multiple issat          ! Use when comparing models 2a and 2b
End

! Model 2b: Equate the means for MZ, DZ and FS separately for males and females
EQ M 1 1 1 M 1 1 2 M 3 1 1 M 3 1 2 M 5 1 1 M 6 1 1 M 6 1 2 M 8 1 1    ! Male mean
EQ M 2 1 1 M 2 1 2 M 4 1 1 M 4 1 2 M 5 1 2 M 7 1 1 M 7 1 2 M 8 1 2    ! Female mean
End

! Model 3: Equate the correlations for DZ and FS pairs
EQ R 3 2 1 R 6 2 1      ! DZM and FSM within-pair correlation
EQ R 4 2 1 R 7 2 1      ! DZF and FSF within-pair correlation
EQ R 5 2 1 R 8 2 1      ! DZOS and FSOS within-pair correlation
End                     ! To compare with full model

! Model 4: Estimates phenotypic correlation between variables (e.g. age)
! This is run independently from the above script
G1: All
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =grpdep.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT t1age1 t1dep1 wgt1 ;
Definition wgt1 /
Begin Matrices;
R Stan nvar nvar     Free     ! Correlation between age and depression
S Diag nvar nvar     Free     ! Standard Deviation of age and depression score
M Full 1 nvar        Free     ! Mean of age and depression score
W Full 1 1                    ! For weight definition variable
End Matrices;
Covariances S*R*S' /
Means M /
Start .1 R 2 1
Start 4 S 1 1
Start 7 S 2 2
Start 13 M 1 1
Start 7 M 1 2
Sp W -1
Weights W /
Options multiple issat
End

Save age.mxs
Get age.mxs
Drop R 1 2 1                  ! To test the significance of the correlation
End
```

B.2. Univariate Models with Sex-limitation and Twin Similarity

```
! Mx script for estimating genetic and environmental parameters for one variable using data
! from 8 zygosity groups in G1219
! A weight to account for possible response/attrition biases in G1219 is included
! A fourth source of variance (U) is estimated to reflect a twin similarity effect
! Means are estimated separately for each sex-specific zygosity
! Sub-models to test for qualitative and quantitative sex differences
! Models 1a and 1b tests for sex differences in type of genetic and shared environmental effects
! Model 2 tests for sex differences in the size of genetic and environmental effects

#Define nvar 1
G1: Male model parameters
Data Calc NGroups=12
Begin Matrices;
X Lower nvar nvar Free          ! Genetic parameters
Y Lower nvar nvar Free          ! Shared environment parameters
Z Lower nvar nvar Free          ! Non-shared environment parameters
U Lower nvar nvar Free          ! Twin similarity parameter
H Diag 1 1                      ! Scalar 0.5 for DZ/FS pairs
End Matrices;
Begin Algebra;
A = X * X';          ! This is going to be Am (Heritability for males)
C = Y * Y';          ! This is going to be Cm (Shared Environment for males)
E = Z * Z';          ! This is going to be Em (Non-shared Environment for males)
T =U * U';           ! This is going to be Tm (Twin Similarity for males)
F= A + C + E + T;
End Algebra;
Start .1 X 1 1
Start .1 Y 1 1
Start .5 Z 1 1
Start .1 U 1 1
Matrix H .5
End

G2: Female model parameters
Data Calc NGroups=12
Begin Matrices;
X Lower nvar nvar Free          ! Genetic parameters
Y Lower nvar nvar Free          ! Shared environment parameters
Z Lower nvar nvar Free          ! Non-shared environment parameters
U Lower nvar nvar Free          ! Twin similarity parameter
H Diag 1 1                      ! Scalar 0.5 for DZ/FS pairs
End Matrices;
Begin Algebra;
A = X * X';          ! This is going to be Am (Heritability for females)
C = Y * Y';          ! This is going to be Cm (Shared Environment for females)
E = Z * Z';          ! This is going to be Em (Non-shared Environment for females)
T =U * U';           ! This is going to be Tm (Twin Similarity for females)
F= A + C + E + T;
End Algebra;
Start .1 X 1 1
Start .1 Y 1 1
Start .5 Z 1 1
Start .1 U 1 1
Matrix H .5
End
```

```
G3: MZM twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =univariate.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 1.00 /
SELECT t1dep1 t1dep2 wgt1;
Definition wgt1 /
Matrices = Group 1
W Full 1 1                          ! For weight definition variable
M Full 1 2 free
End matrices;
Covariances
                ( A + C + E + T | A + C + T
                  A + C + T     | A + C + E + T ) /
Means M;
Start 0 M 1 1 - M 1 2
Sp W -1
Weights W /
Option RSidual
End

G4: MZF twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =univariate.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 3.00 /
SELECT t1dep1 t1dep2 wgt1;
Definition wgt1 /
Matrices = Group 2
W Full 1 1                          ! For weight definition variable
M Full 1 2 free
End matrices;
Covariances
                ( A + C + E + T | A + C + T
                  A + C + T     | A + C + E + T ) /
Means M;
Start 0 M 1 1 - M 1 2
Sp W -1
Weights W /
Option RSidual
End

G5:  DZM twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =univariate.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 2.00 /
SELECT t1dep1 t1dep2 wgt1;
Definition wgt1 /
Matrices = Group 1
W Full 1 1                          ! For weight definition variable
```

```
M Full 1 2 free
End matrices;
Covariances
                    ( A + C + E + T | H@A + C + T _
                      H@A + C + T | A + C + E + T ) /
Means M;
Start 0 M 1 1 - M 1 2
Sp W -1
Weights W /
Option RSidual
End

G6:  DZF twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =univariate.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 4.00 /
SELECT t1dep1 t1dep2 wgt1;
Definition wgt1 /
Matrices = Group 2
W Full 1 1                          ! For weight definition variable
M Full 1 2 free
End matrices;
Covariances
                    ( A + C + E + T | H@A + C + T _
                      H@A + C + T | A + C + E + T ) /
Means M;
Start 0 M 1 1 - M 1 2
Sp W -1
Weights W /
Option RSidual
End

G7:  DZO twin pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =univariate.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 5.00 /
SELECT t1dep1 t1dep2 wgt1;
Definition wgt1 /
Begin Matrices;
X Lower nvar nvar = X1
Y Lower nvar nvar = Y1
Z Lower nvar nvar = Z1
U Lower nvar nvar = U1
A Lower nvar nvar = X2
C Lower nvar nvar = Y2
E Lower nvar nvar = Z2
T Lower nvar nvar = U2
J Diag nvar nvar        ! Genetic correlation between males and females
K Diag nvar nvar        ! Shared environment correlation between males and females
                        ! J OR K are free when testing Models 1a and 1b (below)
W Full 1 1              ! For weight definition variable
```

```
M Full 1 2 free
End matrices;
Covariances
( ( X * X' ) + (Y * Y' ) + ( Z * Z' ) + ( U * U' ) | ( X * J * A' ) + ( Y * K * C' ) + ( U * T' ) _
  ( A * J * X' ) + ( C * K * Y' ) + ( T * U' )      | ( A * A' ) + ( C * C' ) + ( E * E' ) + ( T * T' ) ) /
Means M;
Start 0 M 1 1 - M 1 2
Sp W -1
Weights W /
Value .5 J 1 1 - J nvar nvar
Value 1 K 1 1 - K nvar nvar
Option RSidual
End

G8:  FSM pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =univariate.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 6.00 /
SELECT t1dep1 t1dep2 wgt1;
Definition wgt1 /
Matrices = Group 1
W Full 1 1                    ! For weight definition variable
M Full 1 2 free
End matrices;
Covariances
                (A + C + E      | H@A + C      _
                  H@A + C       | A + C + E    ) /
Means M;
Start 0 M 1 1 - M 1 2
Sp W -1
Weights W /
Option RSidual
End

G9: FSF pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =univariate.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 7.00 /
SELECT t1dep1 t1dep2 wgt1;
Definition wgt1 /
Matrices = Group 2
W Full 1 1                    ! For weight definition variable
M Full 1 2 free
End matrices;
Covariances
                (A + C + E      | H@A + C      _
                  H@A + C       | A + C + E    ) /
Means M;
Start 0 M 1 1 - M 1 2
Sp W -1
Weights W /
```

```
Option RSidual
End

G10:  FSO pairs
Data NINPUT_VARS=20 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =univariate.dat
LABELS id zyg single sex1 sex2 t1age1 t1age2 t2age1 t2age2 t3age1 t3age2 t1dep1 t1dep2
t2dep1 t2dep2 t3dep1 t3dep2 wgt1 wgt2 wgt3
SELECT IF zyg = 8.00 /
SELECT t1dep1 t1dep2 wgt1;
Definition wgt1 /
Begin Matrices;
X Lower nvar nvar = X1
Y Lower nvar nvar = Y1
Z Lower nvar nvar = Z1
A Lower nvar nvar = X2
C Lower nvar nvar = Y2
E Lower nvar nvar = Z2
J Diag   nvar nvar = J7   ! Genetic correlation between males and females
K Diag  nvar nvar = K7  ! Shared environment correlation between males and females
W Full 1 1 =W1
M Full 1 2  free
End matrices
Covariances
        ( ( X * X' ) + ( Y * Y' ) + ( Z * Z' )      | ( X * J * A' ) + ( Y * K * C' )
        ( A * J * X' ) + ( C * K * Y' )             | ( A * A' ) + ( C * C' ) + ( E * E' )      ) /
Means M;
Start 0 M 1 1 - M 1 2
Sp W -1
Weights W /
Option RSidual
End

G11: Standardise Estimates for males
CALCULATION
MATRICES = GROUP 1
Begin Algebra;
G= A%F; !note that this method of standardisation only works for univariate models
S= C%F;
N= E%F;
L= T%F;
End Algebra;
!INTERVALS @95 G 11 1 1  S 11 1 1  N 11 1 1  L 11 1 1
End

G12: Standardise Estimates for females
CALCULATION
MATRICES = GROUP 2
Begin Algebra;
G= A%F;
S= C%F;
N= E%F;
L= T%F;
End Algebra;
!INTERVALS @95 G 12 1 1  S 12 1 1  N 12 1 1 L 12 1 1
!Options Multiple issat
```

```
!Options sat = 3278.56, df = 1502
Options multiple
End

Save sex.mxs
Get sex.mxs

! Model 1a tests for qualitative sex differences in the genetic correlation
! Genetic correlations (J) for DZO and FSO pairs are fixed to 0.5
! This is compared to the above model where J is set free to vary
Fix  J 7 1 1 - J 7 nvar nvar
Value .5 J 7 1 1 - J 7 nvar nvar
End

! Model 1b tests for qualitative sex differences in the shared environmental correlation
! Shared environmental correlations (K) for DZO and FSO pairs are fixed to 1.0
! This is compared to the above model where K is set free to vary
Fix  K 7 1 1 - K 7 nvar nvar
Value 1.0 K 7 1 1 - K 7 nvar nvar
End

! Model 2 tests for quantitative sex differences in the size of parameters
Equate X 1 1 1 X 2 1 1
Equate Y 1 1 1 Y 2 1 1
Equate Z 1 1 1 Z 2 1 1
Equate U 1 1 1 U 2 1 1
End
```

B.3. Cholesky Decomposition for Longitudinal Data

```
! Mx script for estimating common and specific genetic and environmental parameters for three
! variables (representing three time-points) using data from 5 zygosity groups in ECHO
! The first variable is the selection variable to account for the selected nature of the sample
! Means are estimated separately for each sex-specific zygosity
! No sex differences in genetic and environmental parameters are assumed

#Define nvar 3
G1: Male and females model parameters
Data Calc NGroups = 7
Begin Matrices;
X Lower nvar nvar      Free    ! Genetic parameters
Y Lower nvar nvar      Free    ! Shared Environment parameters
Z Lower nvar nvar      Free    ! Non-shared Environment parameters
H Diag 1 1                     ! Scalar 0.5 for DZ/FS pairs
End Matrices;
Begin Algebra;
A= X * X';
C= Y * Y';
E= Z * Z';
P= A + C + E;
End Algebra;
Start .1 X 1 1 - X nvar nvar
Start .1 Y 1 1 - Y nvar nvar
Start .5 Z 1 1 - Z nvar nvar
Matrix H .5
End

G2: MZM twin pairs
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Elongit.dat
LABELS id zyg anx1 anx2 t1dep1 t1dep2 t2dep1 t2dep2
SELECT IF zyg = 1.00 /
SELECT anx1 t1dep1 t2dep1 anx2 t1dep2 t2dep2 /
Matrices = Group 1
M Full 1 6 free
End matrices;
Covariances
                ( A + C + E | A + C   _
                    A + C   | A + C + E ) /
Means M;
Start 0 M 1 1 - M 1 6
Option RSidual
End

G3: MZF twin pairs
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Elongit.dat
LABELS id zyg anx1 anx2 t1dep1 t1dep2 t2dep1 t2dep2
SELECT IF zyg = 2.00 /
SELECT anx1 t1dep1 t2dep1 anx2 t1dep2 t2dep2 /
Matrices = Group 1
M Full 1 6 free
End matrices;
```

```
Covariances
                ( A + C + E | A + C
                  A + C     | A + C + E ) /
Means M;
Start 0 M 1 1 - M 1 6
Option RSidual
End

G4: DZM twin pairs
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Elongit.dat
LABELS id zyg anx1 anx2 t1dep1 t1dep2 t2dep1 t2dep2
SELECT IF zyg = 3.00 /
SELECT anx1 t1dep1 t2dep1 anx2 t1dep2 t2dep2 /
Matrices = Group 1
M Full 1 6 free
End matrices;
Covariances
        ( A + C + E     | H@A + C
        H@A + C         | A + C + E     ) /
Means M;
Start 0 M 1 1 - M 1 6
Option RSidual
End

G5:  DZF twin pairs
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Elongit.dat
LABELS id zyg anx1 anx2 t1dep1 t1dep2 t2dep1 t2dep2
SELECT IF zyg = 4.00 /
SELECT anx1 t1dep1 t2dep1 anx2 t1dep2 t2dep2 /
Matrices = Group 1
M Full 1 6 free
End matrices;
Covariances
        ( A + C + E     | H@A + C
        H@A + C         | A + C + E     ) /
Means M;
Start 0 M 1 1 - M 1 6
Option RSidual
End

G6:  DZO twin pairs
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Elongit.dat
LABELS id zyg anx1 anx2 t1dep1 t1dep2 t2dep1 t2dep2
SELECT IF zyg = 5.00 /
SELECT anx1 t1dep1 t2dep1 anx2 t1dep2 t2dep2 /
Matrices = Group 1
M Full 1 6 free
End matrices;
Covariances
        ( A + C + E     | H@A + C
        H@A + C         | A + C + E     ) /
```

```
Means M;
Start 0 M 1 1 - M 1 6
Option RSidual
End

G7: Calculate genetic / environmental correlations and Standardized Estimates
Data Calc
Matrices = Group 1
I Iden nvar nvar
Begin Algebra;
Q = \sqrt( I . P )~;
T = (Q * X).(Q * X);          ! Squared standardised genetic path estimates
U = (Q * Y).(Q * Y);          ! Squared standardised SE path estimates
V = (Q * Z).(Q * Z);          ! Squared standardised NE path estimates
End Algebra;
!Intervals @95 T 7 1 1 T 7 2 1 T 7 2 2 T 7 3 1 T 7 3 2 T 7 3 3
!Intervals @95 U 7 1 1 U 7 2 1 U 7 2 2 U 7 3 1 U 7 3 2 U 7 3 3
!Intervals @95 V 7 1 1 V 7 2 1 V 7 2 2 V 7 3 1 V 7 3 2 V 7 3 3
Options sat=30219.513, df=11232
End
```

B.4. DeFries-Fulker Extremes Analysis with Sex Differences

```
! Mx script for estimating genetic and environmental parameters in selected extreme group
! using data from 5 zygosity groups in ECHO
! Parameters are estimated separately for males and females
! Model 1 equates parameters across males and females to test for significant sex differences

G1: Model parameters
Data Calc NGroups = 7
Begin Matrices;
A Full 1 1 free          ! Male Genetic parameters
C Full 1 1 free          ! Male Shared Environment parameters
G Full 1 1 free          ! Female Genetic parameters
S Full 1 1 free          ! Female Shared Environment parameters
V Full 1 1 free          ! Residual variance
D Full 1 1 free          ! Difference in variance
R Full 1 1               ! DZ Opposite Sex genetic relatedness index
H Full 1 1               ! Scalar 0.5 for DZ twins
I Full 1 1               ! Scalar 1.0
N Full 1 1               ! Scalar 0
Y Full 1 2               ! Proband status
End Matrices;
Start .1 A 1 1
Start .1 C 1 1
Start .1 G 1 1
Start .1 S 1 1
Start .5 V 1 1
Start 0 D 1 1
Matrix I 1
Matrix R .5
Matrix H .5
Matrix N 0
End

G2: MZ Males
Data NINPUT_VARS=6 NOBSERVATIONS=0
Missing =-99.00
REC File=et1dep.dat
LABELS id zyg t1dep1 t1dep2 proband1 proband2
SELECT if zyg = 1.00 /
SELECT t1dep1 t1dep2 proband1 proband2 /
Definition proband1 proband2 /
Matrices = Group 1
W Full 1 1               ! For weight definition variable
Means  ( A*A+C*C | A*A+C*C ) . Y /
Covariance
        (V | N _
         N | V ) + ( D | N _
                     N | D ) * \v2d(Y) /
Weight W /
Specify Y -2 -1          ! For proband status
Specify W -3
End

G3: DZ Males
Data NINPUT_VARS=6 NOBSERVATIONS=0
Missing =-99.00
```

```
REC File=et1dep.dat
LABELS id zyg t1dep1 t1dep2 proband1 proband2
SELECT if zyg = 3.00 /
SELECT t1dep1 t1dep2 proband1 proband2 /
Definition proband1 proband2 /
Matrices = Group 1
W Full 1 1                  ! For weight definition variable
Means ( H*A*A+C*C | H*A*A+C*C ) . Y  /
Covariance
          (V | N _
           N | V ) + ( D | N _
                       N | D ) * \v2d(Y) /
Weight W /
Specify Y -2 -1             ! For proband status
Specify W -3
End

G4: MZ Females
Data NINPUT_VARS=6 NOBSERVATIONS=0
Missing =-99.00
REC File=et1dep.dat
LABELS id zyg t1dep1 t1dep2 proband1 proband2
SELECT if zyg = 2.00 /
SELECT t1dep1 t1dep2 proband1 proband2 /
Definition proband1 proband2 /
Matrices = Group 1
W Full 1 1                  ! For weight definition variable
Means ( G*G+S*S | G*G+S*S ) . Y /
Covariance
          (V | N _
           N | V ) + ( D | N _
                       N | D ) * \v2d(Y) /
Weight W /
Specify Y -2 -1             ! For proband status
Specify W -3
End

G5: DZ Females
Data NINPUT_VARS=6 NOBSERVATIONS=0
Missing =-99.00
REC File=et1dep.dat
LABELS id zyg t1dep1 t1dep2 proband1 proband2
SELECT if zyg = 4.00 /
SELECT t1dep1 t1dep2 proband1 proband2 /
Definition proband1 proband2 /
Matrices = Group 1
W Full 1 1                  ! For weight definition variable
Means ( H*G*G+S*S | H*G*G+S*S ) . Y  /
Covariance
          (V | N _
           N | V ) + ( D | N _
                       N | D ) * \v2d(Y) /
Weight W /
Specify Y -2 -1             ! For proband status
Specify W -3
End
```

```
G6: DZ Opposite sex (male, female)
Data NINPUT_VARS=6 NOBSERVATIONS=0
Missing =-99.00
REC File=et1dep.dat
LABELS id zyg t1dep1 t1dep2 proband1 proband2
SELECT if zyg = 5.00 /
SELECT t1dep1 t1dep2 proband1 proband2 /
Definition proband1 proband2 /
Matrices = Group 1
Means ( R*A*G+C*S | R*G*A+S*C ) . Y  /
! Residual variance / covariance
Covariance
          (V | N _
           N | V ) + ( D | N _
                       N | D ) * \v2d(Y) /
Weight W /
Specify Y -2 -1            ! For proband status
Specify W -3
End

G7: Standardised estimates
Calculation
Matrices = group 1
Begin Algebra;
Z = A*A _
G*G _
C*C _
S*S _
I-(A*A+C*C) _
I-(G*G+S*S) _
R  /
End Algebra;
Options multiple
Options sat =850.898, df = 555
Intervals @95 Z 1 1 Z 2 1 Z 3 1 Z 4 1 Z 5 1 Z 6 1
End

! Model 1 tests for sex differences in genetic and environmental parameters
Equate A 1 1 1 G 1 1 1
Equate C 1 1 1 S 1 1 1
End
```

B.5. Cholesky Decomposition for Environmental Risk Data

```
! Mx script for estimating genetic, shared and non-shared environmental overlap between
! depression symptoms and negative life events using data from 8 zygosity groups in G1219
! A weight to account for possible response/attrition biases in G1219 is included
! Means are estimated separately for sex-zygosity group
! Scalar to account for variance difference between males and females is incorporated

#Define nvar 2
G1: Male and female model parameters
Data Calc NGroups = 10
Begin Matrices;
X Lower nvar nvar      Free    ! Genetic parameters
Y Lower nvar nvar      Free    ! Shared Environment parameters
Z Lower nvar nvar      Free    ! Non-shared Environment parameters
H Full 1 1                     ! Scalar 0.5 for DZ/FS pairs
End Matrices;
Begin Algebra;
A= X * X' ;                    ! Genetic variance / covariance
C= Y * Y' ;                    ! Shared Environment variance / covariance
E= Z * Z' ;                    ! Non-shared Environment variance / covariance
P= A + C + E ;                 ! Total (phenotypic) variance / covariance
End Algebra;
Start .5 all
Matrix H .5
End

G2: MZM twin pairs
Data NINPUT_VARS=10 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =rgegxe.dat
LABELS id zyg single t2dep1 t2dep2 nle1 nle2 mdis1 mdis2 wgt2
SELECT if  zyg = 1.00
SELECT nle1 t2dep1 nle2 t2dep2 wgt2;
Definition wgt2 /
Matrices= Group 1
W Full 1 1                             ! For weight definition variable
M Full 1 4 free
B Diag 4 4                             ! Scalar for males
End matrices;
Covariances
                B *     ( A + C + E     | A + C          _
                          A + C         | A + C + E      ) * B' /
Means M;
Sp W -1
Weights W /
Sp B 201 200 201 200
Drop @1 201
Start .5 B 2 2 B 4 4
Start 0 M 1 1 to M 1 4
Option RSidual
End

G3: MZF twin pairs
Data NINPUT_VARS=10 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =rgegxe.dat
```

```
LABELS id zyg single t2dep1 t2dep2 nle1 nle2 mdis1 mdis2 wgt2
SELECT if  zyg = 3.00
SELECT nle1 t2dep1 nle2 t2dep2 wgt2;
Definition wgt2 /
Matrices= Group 1
W Full 1 1                                  ! For weight definition variable
M Full 1 4 free
End matrices;
Covariances
                    ( A + C + E      | A + C
                      A + C          | A + C + E      ) /
Means M;
Sp W -1
Weights W /
Start 0 M 1 1 to M 1 4
Option RSidual
End

G4:  DZM twin pairs
Data NINPUT_VARS=10 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =rgegxe.dat
LABELS id zyg single t2dep1 t2dep2 nle1 nle2 mdis1 mdis2 wgt2
SELECT if  zyg = 2.00
SELECT nle1 t2dep1 nle2 t2dep2 wgt2;
Definition wgt2 /
Matrices= Group 1
W Full 1 1                                  ! For weight definition variable
M Full 1 4 free
B Diag 4 4=B2
End matrices;
Covariances
                B *     ( A + C + E      | H@A + C
                          H@A + C        | A + C + E      ) * B' /
Means M;
Sp W -1
Weights W /
Start 0 M 1 1 to M 1 4
Option RSidual
End

G5:  DZF twin pairs
Data NINPUT_VARS=10 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =rgegxe.dat
LABELS id zyg single t2dep1 t2dep2 nle1 nle2 mdis1 mdis2 wgt2
SELECT if zyg = 4.00
SELECT nle1 t2dep1 nle2 t2dep2 wgt2;
Definition wgt2 /
Matrices= Group 1
W Full 1 1                                  ! For weight definition variable
M Full 1 4 free
End matrices;
Covariances
                    ( A + C + E      | H@A + C
                      H@A + C        | A + C + E      ) /
Means M;
```

```
Sp W -1
Weights W /
Start 0 M 1 1 to M 1 4
Option RSidual
End

G6:  DZO twin pairs
Data NINPUT_VARS=10 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =rgegxe.dat
LABELS id zyg single t2dep1 t2dep2 nle1 nle2 mdis1 mdis2 wgt2
SELECT if zyg = 5.00
SELECT nle1 t2dep1 nle2 t2dep2 wgt2;
Definition wgt2 /
Matrices= Group 1
W Full 1 1                              ! For weight definition variable
M Full 1 4 free
B Diag 4 4
End matrices;
Covariances
                B *     ( A + C + E     | H@A + C
                          H@A + C       | A + C + E     )_* B' /
Means M;
Sp W -1
Weights W /
Sp B 300 200 300 300
Drop @1 300
Start .5 B 2 2
Start 0 M 1 1 to M 1 4
Option RSidual
End

G7: FSM sibling pairs
Data NINPUT_VARS=10 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =rgegxe.dat
LABELS id zyg single t2dep1 t2dep2 nle1 nle2 mdis1 mdis2 wgt2
SELECT if zyg = 6.00
SELECT nle1 t2dep1 nle2 t2dep2 wgt2;
Definition wgt2 /
Matrices= Group 1
W Full 1 1                              ! For weight definition variable
M Full 1 4 free
B Diag 4 4 = B2
End matrices;
Covariances
                B *     ( A + C + E     | H@A + C
                          H@A + C       | A + C + E     )_* B' /
Means M;
Sp W -1
Weights W /
Start 0 M 1 1 to M 1 4
Option RSidual
End

G8: FSF sibling pairs
Data NINPUT_VARS=10 NOBSERVATIONS=0
```

```
MISSING =-99.00
REC FILE =rgegxe.dat
LABELS id zyg single t2dep1 t2dep2 nle1 nle2 mdis1 mdis2 wgt2
SELECT if zyg = 7.00
SELECT nle1 t2dep1 nle2 t2dep2 wgt2;
Definition wgt2 /
Matrices= Group 1
W Full 1 1                                  ! for weight definition variable
M Full 1 4 free
End matrices;
Covariances
                ( A + C + E      | H@A + C
                  H@A + C        | A + C + E      ) /
Means M;
Sp W -1
Weights W /
Start 0 M 1 1 to M 1 4
Option RSidual
End

G9: FSO sibling pairs
Data NINPUT_VARS=10 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =rgegxe.dat
LABELS id zyg single t2dep1 t2dep2 nle1 nle2 mdis1 mdis2 wgt2
SELECT if zyg = 8.00
SELECT nle1 t2dep1 nle2 t2dep2 wgt2;
Definition wgt2 /
Matrices= Group 1
W Full 1 1                                  ! for weight definition variable
M Full 1 4 free
B Diag 4 4
End matrices;
Covariances
             B *    ( A + C + E      | H@A + C
                     H@A + C        | A + C + E      ) * B' /
Means M;
Sp W -1
Weights W /
Drop @1 500
Start .5 B 2 2
Start 0 M 1 1 to M 1 4
Option RSidual
End

G10: Calculate genetic / environmental correlations
Data Calc
Matrices = Group 1
I Iden nvar nvar
Begin Algebra;
Q = \sqrt( I . P )~;
T = (Q * X).(Q * X);          ! Squared standardised genetic path estimates
U = (Q * Y).(Q * Y);          ! Squared standardised SE path estimates
V = (Q * Z).(Q * Z);          ! Squared standardised NE path estimates
End Algebra;
Options sat = 12794.487, df = 4921
End
```

B.6. Cholesky Decomposition with Interaction Coeffiecients

```
! Mx script for testing moderation of common and unique genetic, shared and non-shared
! environmental effects on depression using data from G1219
! For brevity only 5 zygosity groups shown
! A weight to account for possible response/attrition biases in G1219 is included
! Means are estimated separately for sex-zygosity group
! Scalar to account for variance difference between males and females is incorporated

Group1: Model parameters
Data Calc NGroups=6
Begin Matrices;
X Full 1 1 free  ! Common genetic parameter on negative life events
Y Full 1 1 free  ! Common genetic parameter on depression
Z Full 1 1 free  ! Unique genetic parameter on depression
T Full 1 1 free  ! Interaction coefficient of common genetic parameter on depression
U Full 1 1 free  ! Interaction coefficient of unique genetic parameter on depression
I Full 1 1 free  ! Common shared environment parameter on negative life events
J Full 1 1 free  ! Common shared environment parameter on depression
K Full 1 1 free  ! Unique shared environment parameter on depression
L Full 1 1 free  ! Interaction coeff of common shared environment parameter on depression
N Full 1 1 free  ! Interaction coeff of unique shared environment parameter on depression
O Full 1 1 free  ! Common non-shared environment parameter on negative life events
P Full 1 1 free  ! Common non-shared environment parameter on depression
Q Full 1 1 free  ! Unique non-shared environment parameter on depression
A Full 1 1 free  ! Interaction coeff of common non-shared environment parameter on depression
G Full 1 1 free  ! Interaction coeff of unique non-shared environment parameter on depression
H Full 1 1       ! Scalar 0.5 for DZ/FS pairs
End Matrices;
Start 0.2 X 1 1 Z 1 1 A 1 1 G 1 1
Start 0.1 Y 1 1 U 1 1 T 1 1 I 1 1 J 1 1 K 1 1 L 1 1
Start 0.8 O 1 1 Q 1 1
Start 0.5 P 1 1
Matrix H 0.5
End

G2: MZM twin pairs
Data NINPUT_VARS=9 NOBSERVATIONS=0
MISSING =-99.00
REC File=nledep.dat
LABELS id zyg nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt2
SELECT if zyg = 1.00 /
SELECT nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt /
Definition rep_nle1 rep_nle2 wgt /
Matrices = Group 1
W Full 1 1          ! For weight definition
R Full 1 1          ! Twin 1 moderator (negative life events)
S full 1 1          ! Twin 2 moderator (negative life events)
M Full 1 4 free     ! Means
B Diag 4 4 free     ! Scalar for males
End matrices;
Covariance
B * ( (X*X | X*(Y+T*R) _ X*(Y+T*R) | (Y+T*R)*(Y+T*R) + (Z+U*R)*(Z+U*R) ) +
    (I*I | I*(J+L*R) _ I*(J+L*R) | (J+L*R)*(J+L*R) + (K+N*R)*(K+N*R) )  +
    (O*O | O*(P+A*R) _ O*(P+A*R) | (P+A*R)*(P+A*R) + (Q+G*R)*(Q+G*R) )  |
    (X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) )' +
    (I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )'  _
```

```
    ( X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) ) +
    (I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )          |
    ( X*X | X*(Y+T*S) _ X*(Y+T*S) | (Y+T*S)*(Y+T*S) + (Z+U*S)*(Z+U*S) ) +
    (I*I | I*(J+L*S) _ I*(J+L*S) | (J+L*S)*(J+L*S) + (K+N*S)*(K+N*S) )  +
    (O*O | O*(P+A*S) _ O*(P+A*S) | (P+A*S)*(P+A*S) + (Q+G*S)*(Q+G*S) ) )* B' /
Means M;
Specify R -1
Specify S -2
Specify W -3
Weights W /
Specify B 201 200 201 200
Drop @1 201
Bound 0 3 B 2 2 B 4 4
Start 0.5 B 2 2 B 4 4
Start 0 M 1 1 - M 1 4
Options RS
End

G3: MZF
Data NINPUT_VARS=9 NOBSERVATIONS=0
MISSING =-99.00
REC File=nledep.dat
LABELS id zyg nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt2
SELECT if zyg = 3.00 /
SELECT nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt /
Definition rep_nle1 rep_nle2 wgt /
Matrices = Group 1
W full 1 1              ! For weight definition
R full 1 1              ! Twin 1 moderator (negative life events)
S full 1 1              ! Twin 2 moderator (negative life events)
M Full 1 4 free         ! Means
End matrices;
Covariance
(X*X | X*(Y+T*R) _ X*(Y+T*R) | (Y+T*R)*(Y+T*R) + (Z+U*R)*(Z+U*R) ) +
(I*I | I*(J+L*R) _ I*(J+L*R) | (J+L*R)*(J+L*R) + (K+N*R)*(K+N*R) )  +
(O*O | O*(P+A*R) _ O*(P+A*R) | (P+A*R)*(P+A*R) + (Q+G*R)*(Q+G*R) )  |
(X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) )' +
(I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )'          _
( X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) ) +
(I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )          |
( X*X | X*(Y+T*S) _ X*(Y+T*S) | (Y+T*S)*(Y+T*S) + (Z+U*S)*(Z+U*S) ) +
(I*I | I*(J+L*S) _ I*(J+L*S) | (J+L*S)*(J+L*S) + (K+N*S)*(K+N*S) )  +
(O*O | O*(P+A*S) _ O*(P+A*S) | (P+A*S)*(P+A*S) + (Q+G*S)*(Q+G*S) /
Means M;
Specify R -1
Specify S -2
Specify W -3
Weights W /
Start 0 M 1 1 - M 1 4
Options RS
End

Group4: DZM
Data NINPUT_VARS=9 NOBSERVATIONS=0
MISSING =-99.00
REC File=nledep.dat
LABELS id zyg nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt2
```

```
SELECT if zyg = 2.00 /
SELECT nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt /
Definition rep_nle1 rep_nle2 wgt /
Matrices= Group 1
W full 1 1              ! For weight definition
R full 1 1              ! Twin 1 moderator (negative life events)
S full 1 1              ! Twin 2 moderator (negative life events)
M Full 1 4 free         ! Means
B Diag 4 4 = B2
End matrices;
Covariance
B * ( (X*X | X*(Y+T*R) _ X*(Y+T*R) | (Y+T*R)*(Y+T*R) + (Z+U*R)*(Z+U*R) ) +
    (I*I | I*(J+L*R) _ I*(J+L*R) | (J+L*R)*(J+L*R) + (K+N*R)*(K+N*R) )  +
    (O*O | O*(P+A*R) _ O*(P+A*R) | (P+A*R)*(P+A*R) + (Q+G*R)*(Q+G*R) ) |
    H@(X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) )' +
    (I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )'   _
    H@( X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) ) +
    (I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )          |
    ( X*X | X*(Y+T*S) _ X*(Y+T*S) | (Y+T*S)*(Y+T*S) + (Z+U*S)*(Z+U*S) ) +
    (I*I | I*(J+L*S) _ I*(J+L*S) | (J+L*S)*(J+L*S) + (K+N*S)*(K+N*S) )  +
    (O*O | O*(P+A*S) _ O*(P+A*S) | (P+A*S)*(P+A*S) + (Q+G*S)*(Q+G*S) ) ) * B' /
Means M;
Specify R -1
Specify S -2
Specify W -3
Weights W /
Start 0 M 1 1 - M 1 4
Options RS
End
```

```
Group5: DZF
Data NINPUT_VARS=9 NOBSERVATIONS=0
MISSING =-99.00
REC File=nledep.dat
LABELS id zyg nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt2
SELECT if zyg = 4.00 /
SELECT nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt /
Definition rep_nle1 rep_nle2 wgt /
Matrices= Group 1
W full 1 1              ! For weight definition
R full 1 1              ! Twin 1 moderator (negative life events)
S full 1 1              ! Twin 2 moderator (negative life events)
M Full 1 4 free         ! Means
End matrices;
Covariance
(X*X | X*(Y+T*R) _ X*(Y+T*R) | (Y+T*R)*(Y+T*R) + (Z+U*R)*(Z+U*R) ) +
(I*I | I*(J+L*R) _ I*(J+L*R) | (J+L*R)*(J+L*R) + (K+N*R)*(K+N*R) )  +
(O*O | O*(P+A*R) _ O*(P+A*R) | (P+A*R)*(P+A*R) + (Q+G*R)*(Q+G*R) ) |
H@(X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) )' +
(I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )'   _
H@( X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) ) +
(I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )      |
( X*X | X*(Y+T*S) _ X*(Y+T*S) | (Y+T*S)*(Y+T*S) + (Z+U*S)*(Z+U*S) ) +
(I*I | I*(J+L*S) _ I*(J+L*S) | (J+L*S)*(J+L*S) + (K+N*S)*(K+N*S) )  +
(O*O | O*(P+A*S) _ O*(P+A*S) | (P+A*S)*(P+A*S) + (Q+G*S)*(Q+G*S) )   /
Means M;
Specify R -1
```

```
Specify S -2
Specify W -3
Weights W /
Start 0 M 1 1 - M 1 4
Options RS
End

Group6: DZO
Data NINPUT_VARS=9 NOBSERVATIONS=0
MISSING =-99.00
REC File=nledep.dat
LABELS id zyg nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt2
SELECT if zyg = 5.00 /
SELECT nle1 dep1 nle2 dep2 rep_nle1 rep_nle2 wgt /
Definition rep_nle1 rep_nle2 wgt /
Matrices= Group 1
W full 1 1              ! For weight definition
R full 1 1              ! Twin 1 moderator (negative life events)
S full 1 1              ! Twin 2 moderator (negative life events)
M Full 1 4 free         ! Means
B Diag 4 4 free         ! Scalar for males
End matrices;
Covariance
B * ( (X*X | X*(Y+T*R) _ X*(Y+T*R) | (Y+T*R)*(Y+T*R) + (Z+U*R)*(Z+U*R) ) +
    (I*I | I*(J+L*R) _ I*(J+L*R) | (J+L*R)*(J+L*R) + (K+N*R)*(K+N*R) )  +
    (O*O | O*(P+A*R) _ O*(P+A*R) | (P+A*R)*(P+A*R) + (Q+G*R)*(Q+G*R) ) |
    H@(X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) )' +
    (I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )'   _
    H@( X*X | X*(Y+T*R) _ X*(Y+T*S) | (Y+T*R)*(Y+T*S) + (Z+U*R)*(Z+U*S) ) +
    (I*I | I*(J+L*R) _ I*(J+L*S) | (J+L*R)*(J+L*S) + (K+N*R)*(K+N*S) )    |
    ( X*X | X*(Y+T*S) _ X*(Y+T*S) | (Y+T*S)*(Y+T*S) + (Z+U*S)*(Z+U*S) ) +
    (I*I | I*(J+L*S) _ I*(J+L*S) | (J+L*S)*(J+L*S) + (K+N*S)*(K+N*S) )  +
    (O*O | O*(P+A*S) _ O*(P+A*S) | (P+A*S)*(P+A*S) + (Q+G*S)*(Q+G*S) ) )* B'  /
Means M;
Specify R -1
Specify S -2
Specify W -3
Weights W /
Specify B 300 200 300 300
Drop @1 300
Start 0 M 1 1 - M 1 4
!Options sat = 12031.197, df = 4627
Options multiple issat
Options RS
End

Save gxe.mxs
Get gxe.mxs
Drop U 1 1 1            !Models 1-6 (Drop T, U, L, N, A, G in turn)
End
```

B.7. Correlated Factors Solution of Cholesky Decomposition

```
! Mx script for examining genetic, shared and non-shared environmental correlations between
! depression and attributional style and proportions of correlation explained by shared factors
! using data from 5 zygosity groups in ECHO
! A selection variable is included to account for the selected nature of the sample
! Means are estimated separately for each zygosity group

G1: Male and Female model parameters
Data Calc NGroups = 6
Begin Matrices;
X Lower nvar nvar       Free    ! Genetic parameters
Y Lower nvar nvar       Free    ! Shared Environment parameters
Z Lower nvar nvar       Free    ! Non-shared Environment parameters
H Full  1 1                     ! Scalar 0.5 used for DZ/FS pairs
End Matrices;
Begin Algebra;
A = X * X' ;
C = Y * Y';
E = Z * Z';
P = A + C + E;
R = \stnd (A);
B = \stnd (C);
D = \stnd (E);
End Algebra;
Start .5 all
Matrix H .5
End

G2: MZM Group
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Ecasq.dat
LABELS id zyg t1dep1 t1dep2 t1casq1 t1casq2 anx1 anx2
SELECT IF zyg = 1.00 /
SELECT anx1 t1dep1 t1casq1 anx2 t1dep2 t1casq2 /
Matrices = Group 1
M FULL 1 6 Free
Covariances
                ( A + C + E | A + C _
                A + C       | A + C + E) /
Means M ;
Start 0 M 1 1 - M 1 6
END

G3: MZF Group
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Ecasq.dat
LABELS id zyg t1dep1 t1dep2 t1casq1 t1casq2 anx1 anx2
SELECT IF zyg = 2.00 /
SELECT anx1 t1dep1 t1casq1 anx2 t1dep2 t1casq2 /
MATRICES = GROUP 1
M FULL 1 6 Free
COVARIANCE
                ( A + C + E | A + C _
                  A + C     | A + C + E) /
```

```
MEANS M ;
Start 0 M 1 1 - M 1 6
END

G4: DZM Group
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Ecasq.dat
LABELS id zyg t1dep1 t1dep2 t1casq1 t1casq2 anx1 anx2
SELECT IF zyg = 3.00 /
SELECT anx1 t1dep1 t1casq1 anx2 t1dep2 t1casq2 /
MATRICES = GROUP 1
M FULL 1 6 Free
H FULL 1 1
COVARIANCE
        (A + C + E      | H@A + C_
        H@A + C         | A + C + E ) /
MEAN M ;
Start 0 M 1 1 - M 1 6
END

G5: DZF Group
Data NINPUT_VARS=8  NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Ecasq.dat
LABELS id zyg t1dep1 t1dep2 t1casq1 t1casq2 anx1 anx2
SELECT IF zyg = 4.00 /
SELECT anx1 t1dep1 t1casq1 anx2 t1dep2 t1casq2 /
MATRICES = GROUP 1
M FULL 1 6 Free
H FULL 1 1
COVARIANCE
        (A + C + E      | H@A + C_
        H@A + C         | A + C + E ) /
MEAN M;
Start 0 M 1 1 - M 1 6
END

G6: DZO Group
Data NINPUT_VARS=8 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =Ecasq.dat
LABELS id zyg t1dep1 t1dep2 t1casq1 t1casq2 anx1 anx2
SELECT IF zyg = 5.00 /
SELECT anx1 t1dep1 t1casq1 anx2 t1dep2 t1casq2 /
MATRICES = GROUP 1
M FULL 1 6 Free
H FULL 1 1
COVARIANCE
        (A + C + E      | H@A + C_
        H@A + C         | A + C + E ) /
MEAN M ;
Start 0 M 1 1 - M 1 6
OPTION RSiduals
!Options sat =30643.017 df = 11395
END
```

B.8. Reciprocal Causation model

```
! Mx script for examining direct effects between depression and attributional style concurrently
! and across time in G1219
! For brevity only 5 zygosity groups shown
! A weight to account for possible response/attrition biases in G1219 is included
! Means are estimated separately for sex-zygosity group
! Scalars to account for variance difference between males and females on both depression and
! attributional style is incorporated

#define nvar 4

G1: Male and Female model parameters
Data Calc NGroups=6
Begin Matrices;
A Diag 4 4 Free          ! Genetic parameters
C Diag 4 4 Free          ! Shared environment parameters
E Diag 4 4 Free          ! Non-shared environment parameters
P Full 8 8               ! Reciprocal causation parameters
I Iden 8 8
R Diag 8 8               ! Measurement error
H Full  1 1              ! Scalar 0.5 for DZ/FS pairs
End Matrices;
Begin Algebra;
Compute A*A';
Compute C*C';
Compute E*E';
End Algebra;
Specify P
0 22 0 0 0 0 0 0
22 0 0 0 0 0 0 0
23 26 0 28 0 0 0 0
24 27 28 0 0 0 0 0
0 0 0 0 0 22 0 0
0 0 0 0 22 0 0 0
0 0 0 0 23 26 0 28
0 0 0 0 24 27 28 0
Specify R
30 31 30 31 30 31 30 31
Start .2 All
Start .1 P 1 1 1 - P 1 8 8 R 1 1 1 - R 1 8 8
Bound 0 1 R 1 1 1 - R 1 8 8
Matrix H .5
End

G2: MZM pairs
Data NINPUT_VARS=11 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =ccasq.dat
LABELS id zyg t1casq1 t1casq2 t1dep1 t1dep2 t2casq1 t2casq2 t2dep1 t2dep2 wgt3
SELECT if  zyg = 1.00
SELECT t1casq1 t1dep1 t2casq1 t2dep1 t1casq2 t1dep2 t2casq2 t2dep2 wgt3 /
Definition wgt3 /
Matrices = Group 1
A Symm 4 4 = %E1       ! Expected covariance matrix from Group 1
C Symm 4 4 = %E1       ! Expected covariance matrix from Group 1
E Symm 4 4 = %E1       ! Expected covariance matrix from Group 1
```

```
W Full 1 1                ! For weight definition
M Full 1 8 Free           ! Means
B Diag 8 8                ! Scalar for males
End matrices;
Covariance      B * ( ((I-P)~ *(A+C+E | A+C _
                                A+C   | A+C+E) *((I-P)~)') + R*R' ) * B' /
Means M;
Specify B 201 200 300 201 201 200 300 201
Drop @1 201
Bound 0 3 K 2 2 K 3 3 K 6 6 K 7 7
Start .5 K 2 2 K 6 6 K 3 3 K 7 7
Start 0 M 1 1 - M 1 8
Specify W -1
Weights W /
Option Rsidual
End

G3: MZF pairs
Data NINPUT_VARS=11 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =ccasq.dat
LABELS id zyg t1casq1 t1casq2 t1dep1 t1dep2 t2casq1 t2casq2 t2dep1 t2dep2 wgt3
SELECT if zyg = 3.00
SELECT t1casq1 t1dep1 t2casq1 t2dep1 t1casq2 t1dep2 t2casq2 t2dep2 wgt3 /
Definition wgt3 /
Matrices = Group 1
A Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
C Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
E Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
W Full 1 1            ! For weight definition
M Full 1 8 Free       ! Means
End matrices;
Covariances     ((I-P)~ *(A+C+E | A+C _
                           A+C   | A+C+E) *((I-P)~)') + R*R' /
Means M;
Specify W -1
Weights W /
Start 0 M 1 1 - M 1 8
Option Rsidual
End

G4: DZM
Data NINPUT_VARS=11 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =ccasq.dat
LABELS id zyg t1casq1 t1casq2 t1dep1 t1dep2 t2casq1 t2casq2 t2dep1 t2dep2 wgt3
SELECT if  zyg = 2.00
SELECT t1casq1 t1dep1 t2casq1 t2dep1 t1casq2 t1dep2 t2casq2 t2dep2 wgt3 /
Definition wgt3 /
Matrices = Group 1
A Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
C Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
E Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
W Full 1 1            ! For weight definition
M Full 1 8 Free       ! Means
B Diag 8 8 = B2       ! Scalar for males
End matrices;
```

```
Covariances     B * (((I-P)~ *(A+C+E | A+C _
                                A+C  | A+C+E) *((I-P)~)') + R*R' ) * B' /
Means M;
Sp W -1
Weights W /
Start 0 M 1 1 - M 1 8
Option Rsidual
End

G5: DZF
Data NINPUT_VARS=11 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =ccasq.dat
LABELS id zyg t1casq1 t1casq2 t1dep1 t1dep2 t2casq1 t2casq2 t2dep1 t2dep2 wgt3
SELECT if  zyg = 4.00
SELECT t1casq1 t1dep1 t2casq1 t2dep1 t1casq2 t1dep2 t2casq2 t2dep2 wgt3 /
Definition wgt3 /
Matrices = Group 1
A Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
C Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
E Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
W Full 1 1            ! For weight definition
M Full 1 8 Free       ! Means
End matrices;
Covariances     ((I-P)~ *(A+C+E | A+C _
                          A+C  | A+C+E) *((I-P)~)') + R*R' /
Means M;
Sp W -1
Weights W /
Start 0 M 1 1 - M 1 8
Option Rsiduals
End

G6: DZO
Data NINPUT_VARS=11 NOBSERVATIONS=0
MISSING =-99.00
REC FILE =ccasq.dat
LABELS id zyg t1casq1 t1casq2 t1dep1 t1dep2 t2casq1 t2casq2 t2dep1 t2dep2 wgt3
SELECT if  zyg = 5.00
SELECT t1casq1 t1dep1 t2casq1 t2dep1 t1casq2 t1dep2 t2casq2 t2dep2 wgt3 /
Definition wgt3 /
Matrices = Group 1
A Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
C Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
E Symm 4 4 = %E1      ! Expected covariance matrix from Group 1
W Full 1 1            ! For weight definition
M Full 1 8 Free       ! Means
B Diag 8 8            ! Scalar for males
End matrices;
Covariances     B * ( ((I-P)~ *(A+C+E | A+C _
                                A+C  | A+C+E) *((I-P)~)') + R*R' ) * B' /
Means M;
Specify B 400 200 300 400 400 400 400 400
Drop @1 400
Bound 0 3 K 2 2 K 3 3
Start .5 K 2 2 K 3 3
Start 0 M 1 1 - M 1 8
```

```
Specify W -1
Weights W /
Options multiple issat
!Options sat = 15227.382, df = 6182
Option Rsidual
End

Save causal.mxs

Get causal.mxs
Drop P 2 3 1          ! Time 1 Attributional style -> Time 2 Attributional style
End

Get causal.mxs
Drop P 2 4 1          ! Time 1 Attributional style -> Time 2 Depression
End

Get causal.mxs
Drop P 2 3 2          ! Time 1 Depression -> Time 2 Attributional style
End

Get causal.mxs
Drop P 2 4 2          ! Time 1 Depression -> Time 2 Depression
End
```

B.9. Path model

```
! Mx script for examining mediating/moderating and correlational/direct paths between
! 11 variables across time in ECHO
! A weight to account for possible response/attrition biases in ECHO is included
! Means are estimated separately for males and females for some variables

G1: Model Parameters
Data Calc NGroups=4
Begin Matrices;
S Symm 22 22          ! S contains variance and covariance/correlations between variables
A Full 22 22          ! A contains the direct paths (causal effects) between variables
F Full 11 22          ! This is used for the algebra
I Iden 22 22
U Unit  11 1
End Matrices;
Specify S
1                ! Variables 1-11 are manifest variables (variances need to be estimated)
12 2
13 14 3          ! Correlations between variables estimated here (parameters 12-17)
0 0 0 0
0 0 0 0 0
0 0 0 0 0 4
0 0 0 0 0 15 5
0 0 0 0 0 0 0 6
0 0 0 0 0 0 0 0 7
0 0 0 0 0 0 0 0 0 8
0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0                ! Variance of latent factors constrained to be 1
0 0 0 0 0 0 0 0 0 0 0 0 0 0 9
0 0 0 0 0 0 0 0 0 0 0 0 0 0 16 10
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 11
Label Row S
M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 L1 L2 L3 L4 L5 L6 L7 L8 L9 L10 L11
Label Col S
M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 L1 L2 L3 L4 L5 L6 L7 L8 L9 L10 L11
Specify A        ! This matrix contains loadings of manifest on latent variables (direct paths)
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 ! No effects are estimated between manifest variables
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
16 19 0 0 0 0 0 0 0 0 0 0 0 100 0 0 0 0 0 0 0     ! Observed variables on latent variables = 1
17 30 21 0 0 0 0 0 0 0 0 0 0 0 100 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
18 20 22 23 24 25 26 27 28 29 0 0 0 0 0 0 0 0 0 0 0 100 ! Test 27, 28 OR 29 at any one time
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
```

```
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Drop @1 100
Label Row A
M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 L1 L2 L3 L4 L5 L6 L7 L8 L9 L10 L11
Label Col A
M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 L1 L2 L3 L4 L5 L6 L7 L8 L9 L10 L11

Specify F
100 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 100 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 100 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 100 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 100 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 100 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 100 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 100 0 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 100 0 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 100 0 0 0 0 0 0 0 0 0 0 0 0
0 0 0 0 0 0 0 0 0 0 100 0 0 0 0 0 0 0 0 0 0 0
Drop @1 100

Label Row F
M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11
Label Col F
M1 M2 M3 M4 M5 M6 M7 M8 M9 M10 M11 L1 L2 L3 L4 L5 L6 L7 L8 L9 L10 L11

Begin Algebra;
C =  F & ((I - A)~ & S);            ! Covariance
End Algebra;
Start 1 S 1 1 S 2 2 S 3 3 S 6 6 S 7 7 S 8 8 S 9 9 S 10 10
Start .8 S 15 15 S 16 16
Start .7 S 22 22
Start -.1 S 2 1 S 3 2
Start .1 S 3 1 S 7 6
Start -.1 A 5 1 A 4 2 A 5 3 A 11 2
Start .1 A 4 1 A 11 1 A 11 4 A 5 2
Start .2 A 11 3
Start -.4 A 11 5
!Start .1  A 11 8
Start -.1 A 11 9
!Start .1 A 11 10
Start .2 A 11 6 A 11 7
Options RSidual
End

G2: Data group for males
Data NINPUT_VARS=17 NOBSERVATIONS=0
Missing =-99.00
REC file=ECHOinteraction3.DAT
```

```
LABELS ID SINGLE SEX1 SEX2 ZYG MDIS SES FAMTYP ATTST MATDEP NLE
GRISK DEP MDXNL ASXNL GXNLE WGT
SELECT if sex1 = 1.00
SELECT FAMTYP SES MDIS MATDEP ATTST GRISK NLE MDXNL ASXNL GXNLE
DEP WGT /
Definition_variables  WGT /
Matrices = group 1
W Full 1 1                ! For weight definition
M Full 1 11 Free          ! Means
Covariance C;
Means M;
Weights W;
Specify M
31 32 33 34 35 36 37 38 39 40 41
Start 0 M 1 1 to M 1 11
Options NO_Output
End

G3: Data group for females
Data NINPUT_VARS=17 NOBSERVATIONS=0
Missing =-99.00
REC file=ECHOinteraction3.DAT
LABELS ID SINGLE SEX1 SEX2 ZYG MDIS SES FAMTYP ATTST MATDEP NLE
GRISK DEP MDXNL ASXNL GXNLE WGT
SELECT if sex1 = 0.00
SELECT FAMTYP SES MDIS MATDEP ATTST GRISK NLE MDXNL ASXNL GXNLE
DEP WGT /
Definition_variables WGT /
Matrices = group 1
W Full 1 1                ! For weight definition
M Full 1 11 Free          ! Means
Covariance C;
Means M;
Weights W;
Specify M
31 32 43 34 44 36 37 38 45 40 41
Start 0 M 1 1 to M 1 11
!Intervals @95 A 1 4 1 A 1 5 1 A 1 5 3 A 1 11 4 A 1 11 5 A 1 11 6 A 1 11 9
!Intervals @95 S 1 2 1
!Intervals @95 S 1 3 2 S 1 7 6
End

G4: Constrain Phenotypic variances to 1
Data Constraint
Begin Matrices = Group 1
Q Unit 1 11
C comp 11 11 =C1
End Matrices;
Constraint \d2v(C) = Q;
Options multiple issat
!Options sat = 15588.113, df = 5833
End
```

Appendix C: Tables

Table C.1a: Testing group differences in means and covariances between males and females and zygosity groups for ECHO depression data

Models	-2LL	df	χ^2	df	p	AIC
ECHO Wave 1 Depression data						
Full Saturated Model[a]	114873.33	18413	---	---	---	---
Model 1a	114876.30	18421	---	---	---	---
Model 1b[b]	114879.03	18422	2.73	1	0.10	0.73
Model 2a	114875.24	18419	---	---	---	---
Model 2b[c]	114876.30	18421	1.06	2	0.59	-2.95
ECHO Wave 2 Depression data						
Full Saturated Model[a]	112568.12	18109	---	---	---	---
Model 1a	112575.33	18117	---	---	---	---
Model 1b[b]	112577.11	18118	1.78	1	0.18	-0.22
Model 2a	112572.39	18115	---	---	---	---
Model 2b[c]	112575.33	18117	2.94	2	0.23	-1.06

[a] *The full saturated model estimates means, variances and covariances separately by sex-specific zygosity groups and is used for a basis of comparison for models assuming groups differences, and for the calculation of subsequent genetic models*

[b] *A significant deterioration in fit indexed by the difference in χ^2 between Models 1a and 1b is indicative of mean sex differences in depression*

[c] *A significant deterioration in fit indexed by the difference in χ^2 between Models 2a and 2b is indicative of mean zygosity differences in depression*

Table C.1b: Testing group differences in means and covariances between males and females and zygosity groups for G1219 depression data

Models	-2LL	Df	χ^2	df	p	AIC
G1219 Wave 1 Depression data						
Full Saturated Model[a]	12369.54	5615	---	---	---	---
Model 1a	12452.57	5629	---	---	---	---
Model 1b[b]	12497.55	5630	44.99	1	< 0.001	42.99
Model 2a	12390.82	5625	---	---	---	---
Model 2b[c]	12452.57	5629	61.74	4	<0.001	53.74
Model 3 [d]	12414.44	5618	44.91	3	<0.001	38.91
G1219 Wave 2 Depression data						
Full Saturated Model[a]	8246.25	4089	---	---	---	---
Model 1a	8305.06	4103	---	---	---	---
Model 1b[b]	8382.00	4104	76.94	1	<0.001	74.94
Model 2a	8250.25	4099	---	---	---	---
Model 2b[c]	8305.06	4103	54.81	4	<0.001	46.81
Model 3[d]	8250.70	4092	4.45	3	0.21	-1.55
G1219 Wave 3 Depression data						
Full Saturated Model[a]	4274.58	2484	---	---	---	---
Model 1a	4295.51	2498	---	---	---	---
Model 1b[b]	4373.23	2499	77.72	1	<0.001	75.72
Model 2a	4275.71	2494	---	---	---	---
Model 2b[c]	4295.51	2498	19.80	4	<0.001	11.80
Model 3[d]	4288.10	2487	13.52	3	0.004	7.52

[a] *The full saturated model estimates means, variances and covariances separately by sex-specific zygosity groups and is used for a basis of comparison for models assuming groups differences, and for the calculation of subsequent genetic models*

[b] *A significant deterioration in fit indexed by the difference in χ^2 between Models 1a and 1b is indicative of mean sex differences in depression*

[c] *A significant deterioration in fit indexed by the difference in χ^2 between Models 2a and 2b is indicative of mean zygosity differences in depression*

[d] *A significant deterioration in fit indexed by the difference in χ^2 between Model 3 and the full saturated model is indicative of differences in within-pair covariance between DZ and FS pairs*

Table C.2: Testing qualitative, quantitative and scalar sex differences in genetic and environmental influences for G1219 depression data

Models	-2LL	df	χ^2	df	p	AIC	RMSEA
G1219 Wave 1 Depression data							
Full Saturated Model[a]	9494.70	3487	---	---	---	---	---
Model 1[b]	9530.82	3504	36.12	17	<0.01	2.12	0.13
Model 2[c]	9530.82	3504	36.12	17	<0.01	2.12	0.13
Model 3[d]	9530.82	3505	36.12	18	0.01	0.12	0.02
Model 4[e]	**9529.34**	**3507**	**34.64**	**20**	**0.02**	**-5.36**	**0.02**
Model 5[f]	9533.27	3508	38.57	21	0.01	-3.43	0.02
G1219 Wave 2 Depression data							
Full Saturated Model[a]	6197.46	2471	---	---	---	---	---
Model 1[b]	6232.70	2488	35.24	17	0.01	1.24	0.03
Model 2[c]	6232.70	2488	35.24	17	0.01	1.24	0.03
Model 3[d]	6232.70	2489	35.24	18	<0.01	-0.76	0.03
Model 4[e]	**6229.44**	**2491**	**31.98**	**20**	**0.04**	**-8.02**	**0.02**
Model 5[f]	6234.31	2492	36.48	21	0.02	-5.16	0.02
G1219 Wave 3 Depression data							
Full Saturated Model[a]	3222.41	1502	---	---	---	---	---
Model 1[b]	3238.08	1519	15.67	17	0.55	-18.33	Incalculable
Model 2[c]	3238.08	1519	15.67	17	0.55	-18.33	Incalculable
Model 3[d]	3238.08	1520	15.67	18	0.62	-20.33	Incalculable
Model 4[e]	3239.72	1522	17.31	20	0.63	-22.69	Incalculable
Model 5[f]	**3239.77**	**1523**	**17.36**	**21**	**0.69**	**-24.64**	Incalculable

[a] *The full saturated model is used for the calculation of subsequent genetic models*
[b] *This allows the genetic relatedness between opposite sex-pair twins and siblings to deviate from the specified value of 0.5*
[c] *This allows the shared environmental relatedness between opposite sex-pair twins and siblings to deviate from the specified value of 1.0*
[d] *This allows for sex differences in the size of genetic and environmental influences*
[e] *This assumes variance differences between males and females*
[f] *This assumes no sex differences between males and females*

Table C.3: Model-fitting results of De-Fries-Fulker extremes analysis of Waves 1, 2 and 3 G1219 depression measures

Models	-2LL	df	χ^2	df	p	AIC	RMSEA
G1219 Wave 1 Depression data							
Full Saturated Model[a]	6489.00	3052	---	---	---	---	---
Model 1[b]	6514.90	3070	25.91	18	0.10	-10.09	0.04
Model 2[c]	**6581.77**	**3072**	**30.76**	**20**	**0.06**	**-9.24**	**0.05**
G1219 Wave 2 Depression data							
Full Saturated Model[a]	4314.09	2334	---	---	---	---	---
Model 1[b]	**4346.92**	**2352**	**32.83**	**18**	**0.02**	**-3.17**	**0.08**
Model 2[c]	4360.32	2354	46.23	20	0.001	6.23	0.10
G1219 Wave 3 Depression data							
Full Saturated Model[a]	2150.85	1374	---	---	---	---	---
Model 1[b]	2167.80	1392	16.96	18	0.53	-19.05	Incalculable
Model 2[c]	**2169.65**	**1394**	**18.80**	**20**	**0.54**	**-21.20**	**Incalculable**

[a] *The full saturated model is used for the calculation of subsequent genetic models*
[b] *This allows for sex differences in the size of genetic and environmental influences*
[c] *This assumes no sex differences between males and females*

Table C.4: Testing group differences in means and covariances between males and females, and zygosity groups for G1219 Wave 2 negative life events and maternal punitive discipline data

Models	-2LL	df	χ^2	df	p	AIC
G1219 Negative Life Events data						
Full Saturated Model[a]	6450.58	4090	---	---	---	---
Model 1a	6465.04	4104	---	---	---	---
Model 1b[b]	6465.04	4105	0.24	1	0.63	-1.76
Model 2a	6453.03	4100	---	---	---	---
Model 2b[c]	6465.05	4104	12.02	4	0.02	4.02
Model 3[d]	6467.43	4093	16.85	3	0.001	10.85
G1219 Maternal Punitive Discipline data						
Full Saturated Model[a]	19873.08	3830	---	---	---	---
Model 1a	19916.15	3844	---	---	---	---
Model 1b[b]	19916.37	3845	0.22	1	0.64	-1.78
Model 2a	19887.45	3840	---	---	---	---
Model 2b[c]	19916.15	3844	28.70	4	<0.001	20.78
Model 3[d]	19875.68	3833	2.61	3	0.46	-3.40

[a] *The full saturated model estimates means, variances and covariances separately by sex-specific zygosity groups and is used for a basis of comparison for models assuming groups differences, and for the calculation of subsequent genetic models*

[b] *A significant deterioration in fit indexed by the difference in χ^2 between Models 1a and 1b is indicative of mean sex differences in depression*

[c] *A significant deterioration in fit indexed by the difference in χ^2 between Models 2a and 2b is indicative of mean zygosity differences in depression*

[d] *A significant deterioration in fit indexed by the difference in χ^2 between Model 3 and the full saturated model is indicative of differences in within-pair covariance between DZ and FS pairs*

Table C.5: Testing qualitative, quantitative and scalar sex differences in genetic and environmental influences for G1219 negative life events and maternal punitive discipline data

Models	-2LL	df	χ^2	df	p	AIC	RMSEA
Negative Life Events data							
Full Saturated Model[a]	6257.49	2482	---	---	---	---	---
Model 1[b]	6274.20	2499	16.71	17	0.47	-17.29	Incalculable
Model 2[c]	6274.20	2499	16.71	17	0.47	-17.29	Incalculable
Model 3[d]	6274.20	2500	16.71	18	0.54	-19.29	Incalculable
Model 4[e]	6275.97	2502	18.48	20	0.56	-21.52	Incalculable
Model 5[f]	**6276.37**	**2503**	**18.89**	**21**	**0.59**	**-23.11**	**Incalculable**
Maternal Punitive Discipline data							
Full Saturated Model[a]	5890.96	2331	---	---	---	---	---
Model 1[b]	5902.84	2348	11.87	17	0.81	-22.13	Incalculable
Model 2[c]	5902.84	2348	11.87	17	0.81	-22.13	Incalculable
Model 3[d]	5902.84	2349	11.87	18	0.85	-24.13	Incalculable
Model 4[e]	5904.64	2351	13.68	20	0.85	-26.33	Incalculable
Model 5[f]	**5904.73**	**2352**	**13.77**	**21**	**0.88**	**-28.23**	**Incalculable**

[a] *The full saturated model is used for the calculation of subsequent genetic models*
[b] *This allows the genetic relatedness between opposite sex-pair twins and siblings to deviate from the specified value of 0.5*
[c] *This allows the shared environmental relatedness between opposite sex-pair twins and siblings to deviate from the specified value of 1.0*
[d] *This allows for sex differences in the size of genetic and environmental influences*
[e] *This assumes variance differences between males and females*
[f] *This assumes no sex differences between males and females*

Table C.6: Testing group differences in means and covariances between males and females and zygosity groups for G1219 Waves 1 and 2 and Echo Wave 1 attributional style data

Models	-2LL	Df	χ^2	df	p	AIC
Echo Wave 1 Attributional style data						
Full Saturated Model[a]	113085.57	18358	---	---	---	---
Model 1a	113089.65	18366	---	---	---	---
Model 1b[b]	113097.60	18367	7.96	1	<0.01	5.96
Model 2a	113089.61	18364	---	---	---	---
Model 2b[c]	113089.64	18366	0.03	2	0.98	-3.97
G1219 Wave 1 Attributional style data						
Full Saturated Model[a]	19617.16	3971	---	---	---	---
Model 1a	19636.42	3985	---	---	---	---
Model 1b[b]	19645.85	3986	9.43	1	< 0.01	7.43
Model 2a	19621.31	3981	---	---	---	---
Model 2b[c]	19636.42	3985	15.11	4	<0.01	7.11
Model 3 [d]	19619.22	3974	2.06	3	0.56	-3.94
G1219 Wave 2 Attributional style data						
Full Saturated Model[a]	11543.70	2446	---	---	---	---
Model 1a	11550.19	2460	---	---	---	---
Model 1b[b]	11551.47	2461	1.29	1	0.26	-0.71
Model 2a	11546.73	2456	---	---	---	---
Model 2b[c]	11550.19	2460	3.45	4	0.49	-4.55
Model 3[d]	11543.99	2449	0.29	3	0.29	-5.71

[a] *The full saturated model estimates means, variances and covariances separately by sex-specific zygosity groups and is used for a basis of comparison for models assuming groups differences, and for the calculation of subsequent genetic models*

[b] *A significant deterioration in fit indexed by the difference in χ^2 between Models 1a and 1b is indicative of mean sex differences in depression*

[c] *A significant deterioration in fit indexed by the difference in χ^2 between Models 2a and 2b is indicative of mean zygosity differences in depression*

[d] *A significant deterioration in fit indexed by the difference in χ^2 between Model 3 and the full saturated model is indicative of differences in within-pair covariance between DZ and FS pairs*

Table C.7: Testing qualitative, quantitative and scalar sex differences in genetic and environmental influences for G1219 attributional style data

Models	-2LL	df	χ^2	df	p	AIC	RMSEA
Wave 2 Attributional style data							
Full Saturated Model[a]	6132.91	2408	---	---	---	---	---
Model 1[b]	6147.83	2425	14.92	17	0.60	-19.08	Incalculable
Model 2[c]	6147.83	2425	14.92	17	0.60	-19.08	Incalculable
Model 3[d]	6147.83	2426	14.92	18	0.67	-21.08	Incalculable
Model 4[e]	6151.92	2428	19.01	20	0.52	-20.99	Incalculable
Model 5[f]	**6151.99**	**2429**	**19.08**	**21**	**0.58**	**-22.92**	**Incalculable**
Wave 3 Attributional Style data							
Full Saturated Model[a]	3261.47	1481	---	---	---	---	---
Model 1[b]	3276.92	1498	15.45	17	0.56	-18.55	Incalculable
Model 2[c]	3276.92	1498	15.45	17	0.56	-18.55	Incalculable
Model 3[d]	3276.92	1499	15.45	18	0.63	-20.55	Incalculable
Model 4[e]	**3273.67**	**1501**	**12.20**	**20**	**0.91**	**-27.80**	**Incalculable**
Model 5[f]	3279.47	1502	18.00	21	0.65	-24.00	Incalculable

[a] *The full saturated model is used for the calculation of subsequent genetic models*
[b] *This allows the genetic relatedness between opposite sex-pair twins and siblings to deviate from the specified value of 0.5*
[c] *This allows the shared environmental relatedness between opposite sex-pair twins and siblings to deviate from the specified value of 1.0*
[d] *This allows for sex differences in the size of genetic and environmental influences*
[e] *This assumes variance differences between males and females*
[f] *This assumes no sex differences between males and females*

Table C.8: Model-fitting results of testing directional paths between attributional style and depression

Models	-2LL	Df	$\Delta\chi^2$	Δdf	p
Wave 2 Attributional style					
Full Model (8 paths)[a]	15586.89	6458	---	---	---
Sub-Model 1 (Drop p_{C1})[b]	15847.37	6459	260.47	1	< 0.001
Sub-Model 2 (Drop p_{C2})[c]	15632.10	6459	45.20	1	< 0.001
Sub-Model 3 (Drop p_{L1})[d]	15652.96	6459	66.06	1	< 0.001
Sub-Model 4 (Drop p_{L2})[e]	15597.62	6459	10.72	1	< 0.01
Sub-Model 5 (Drop p_{L3})[f]	15594.02	6459	7.12	1	< 0.01
Sub-Model 6 (Drop p_{L4})[g]	15621.70	6459	34.80	1	< 0.001
Sub-Model 7 (Drop E_{AS})[h]	15602.79	6459	15.90	1	< 0.001
Sub-Model 7 (Drop E_{DEP})[i]	15597.15	6459	10.25	1	< 0.01

[a] *The full phenotypic causal model contains 8 paths*
[b] *This excludes the parameter representing concurrent effects between attributional style and depression at Time 1*
[c] *This excludes the parameter representing concurrent effects between attributional style and depression at Time 2*
[d] *This excludes the parameter representing stability of attributional style between Time 1 and Time 2*
[e] *This excludes the parameter representing causal effects between Attributional Style at Time 1 and Depression at Time 2*
[f] *This excludes the parameter representing causal effects between Depression at Time 1 and Attributional Style at Time 2*
[g] *This excludes the parameter representing stability of depression between Time 1 and Time 2*
[h] *This excludes the parameter representing measurement error of Attributional Style at Time 1 and 2*
[i] *This excludes the parameter representing measurement error of Depression at Time 1 and 2*

Table C.9: Results of testing path estimates in Models 1, 2 and 3 for the G1219 and Echo samples

G1219			Echo		
Model	**Path tested**	**$\Delta\chi^2(1)$**	**Model**	**Path tested**	**$\Delta\chi^2(1)$**
1	Maternal Punitive Discipline x Negative Life events Interaction	2.63, p = n.s.	1	Maternal Depression x Negative Life events Interaction	1.04, p = n.s.
2	Attributional style x Negative Life events Interaction	1.97, p = n.s.	2	Attributional style x Negative Life events Interaction	5.74, p < 0.05
3	Genetic Risk x Negative Life events Interaction	0.68, p = n.s.	3	Genetic Risk x Negative Life events Interaction	0.22, p = n.s.
4	Correlation: Maternal Neuroticism and Wave 1 Genetic Risk	59.45, p < 0.001	4	Correlation: Family Composition and Socioeconomic Status	43.37, p < 0.001
	Correlation: Maternal Neuroticism and Family Chronic Stress	254.81, p < 0.001		Correlation: Family Composition and Maternal Punitive Discipline	1.68, p = n.s.
	Correlation: Family Chronic Stress and Wave 1 Genetic Risk	49.75, p < 0.001		Correlation: Socioeconomic Status and Maternal Discipline	14.46, p < 0.001
	Correlation: Negative Life Events and Wave 3 Genetic Risk	56.87, p < 0.001		Correlation: Negative Life Events and Genetic Risk	5.51, p < 0.05
	Maternal Neuroticism to Maternal Punitive Discipline	4.84, p < 0.05		Family composition to Maternal Depression	9.23, p < 0.01
	Maternal Neuroticism to Wave 2 Depression	3.16, p = 0.08		Family composition to Attributional Style	4.03, p < 0.05
	Maternal Neuroticism to Attributional Style	2.49, p = n.s.		Family composition to Depression	2.16, p = n.s.
	Maternal Neuroticism to Wave 3 Depression	3.13, p = 0.08		Socioeconomic Status to Maternal Depression	0.64, p = n.s.
	Wave 1 Genetic Risk to Wave 1 Depression	491.52, p < 0.001		Socioeconomic Status to Depression	0.25, p = n.s.
	Wave 1 Genetic Risk to	0.71, p = n.s.		Socioeconomic Status to	2.27, p = n.s.

Attributional Style		Attributional Style	
Wave 1 Depression to Maternal Punitive Discipline	64.35, $p < 0.001$	Maternal Punitive Discipline to Attributional Style	7.23, $p < 0.01$.
Wave 1 Depression to Wave 2 Depression	518.91, $p < 0.001$	Maternal Punitive Discipline to Depression	0.78, p = n.s.
Wave 1 Depression to Attributional Style	165.43, $p < 0.001$	Maternal Depression to Depression	3.96, $p < 0.05$.
Family chronic stress to Maternal Punitive Discipline	7.16, $p < 0.05$	Attributional Style to Depression	113.28, $p < 0.001$
Family chronic stress to Wave 2 Depression	2.82, p = n.s.	Genetic Risk to Depression	8.73, $p < 0.05$
Family chronic stress to Attributional Style	0.17, p = n.s.	Negative Life Events to Depression	1.52, p = n.s.
Family chronic stress to Wave 3 Depression	3.48, p = 0.06		
Maternal Punitive Discipline to Wave 3 Depression	0.15, p = n.s.		
Wave 2 Genetic risk to Wave 2 Depression	81.17, $p < 0.001$		
Wave 2 Depression to Wave 3 Depression	197.23, $p < 0.001$		
Attributional Style to Wave 3 Depression	5.41, $p < 0.05$		
Wave 3 Genetic Risk to Wave 3 Depression	43.23, $p < 0.001$		
Negative Life events to Wave 3 Depression	96.48, $p < 0.001$		

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